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(71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD-0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064 (US).

(72) Inventors: DAILEY, Stephen, H. ; 472 Tyler Court, Vernon Hills, IL 60061 (US). DESAI, Suresh, M. ; 1408 Amy Lane, Libertyville, IL 60048 (US). DEVARE, Sushil, G. ; 2492 Farnsworth Lane, Northbrook, IL 60062 (US).

(74) Agents: GORMAN, Edward, H., Jr. et al.; Abbott Laboratories, CHAD D-377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).

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(54) Title: HEPATITIS C ASSAY UTILIZING RECOMBINANT ANTIGENS TO NS1

(57) Abstract

The present invention provides unique recombinant antigens representing distinct antigenic regions of the NS1 region of the HCV genome which can be used as reagents for the detection of antibodies and antigen in body fluids from individuals exposed to hepatitis C virus (HCV). The present invention also provides an assay for detecting the presence of an antibody to an HCV antigen in a sample by contacting the sample with the recombinant antigens. Preferred assay formats include a screening assay, a confirmatory assay, a competition or neutralization assay and an immunodot assay.

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HEPATITIS C ASSAY UTILIZING RECOMBINANT ANTIGENS TO NS1

This is a continuation-in-part application of U.S. Serial No. 07/572,822, filed August 24, 1990 and U.S. Serial No. 07,614,069, filed November 7, 1990, which enjoy common ownership and are incorporated herein by reference. This application also is related to co-filed patent applicationS entitled "HEPATITIS C ASSAY UTILIZING RECOMBINANT ANTIGENS FROM NS5 REGION"(U. S. Serial No. 748,565) and "HEPATITIS C ASSAY UTILIZING RECOMBINANT ANTIGENS TO C-100 REGION"(U. S. Serial No. 748,566) which enjoy common ownership and are incorporated herein by reference.

This invention relates generally to an assay for identifying the presence in a sample of an antibody which is immunologically reactive with a hepatitis C virus antigen and specifically to an assay for detecting a complex of an antibody and recombinant antigens representing distinct regions of the HCV genome. Recombinant antigens derived from the molecular cloning and expression in a heterologous expression system of the synthetic DNA sequences representing distinct antigenic regions of the HCV genome can be used as reagents for the detection of antibodies and antigen in body fluids from individuals exposed to hepatitis C virus (HCV).

BACKGROUND OF THE INVENTION

Acute viral hepatitis is clinically diagnosed by a well-defined set of patient symptoms, including jaundice, hepatic tenderness, and an increase in the serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase. Additional serologic immunoassays are generally performed to diagnose the specific type of viral causative agent. Historically, patients presenting clinical hepatitis symptoms and not otherwise infected by hepatitis A, hepatitis B, Epstein-Barr or cytomegalovirus were clinically diagnosed as having non-A non-B hepatitis (NANBH) by default. The disease may result in chronic liver damage.

Each of the well-known, immunologically characterized hepatitis-inducing viruses, hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis D virus (HDV) belongs to a separate family of viruses and has a distinctive viral organization, protein structure, and mode of replication.

Attempts to identify the NANBH virus by virtue of genomic similarity to one of the known hepatitis viruses have failed, suggesting that NANBH has a distinct organization and structure. [Fowler, et al., J. Med. Virol., 12:205-213 (1983) and Weiner, et al., J. Med. Virol., 21:239-247 (1987)].

Progress in developing assays to detect antibodies specific for NANBH has

been particularly hampered by difficulties in correctly identifying antigens associated with NANBH. See, for example, Wands, J., et al., U.S. Patent 4,870,076, Wands, et al., Proc. Nat'l. Acad. Sci., 83:6608-6612 (1986), Ohori, et al., J. Med. Virol., 12:161-178 (1983), Bradley, et al., Proc. Nat'l. Acad. Sci., 84:6277-6281, (1987), Akatsuka, T., et al., J. Med. Virol, 20:43-56 (1986), Seto, B., et al., U.S. Patent Application Number 07/234,641 (available from U.S. Department of Commerce National Technical Information Service, Springfield, Virginia, No. 89138168), Takahashi, K., et al., European Patent Application No. 0 293 274, published November 30, 1988, and Seelig, R., et al., in PCT Application PCT/EP88/00123.

Recently, another hepatitis-inducing virus has been unequivocally identified as hepatitis C virus (HCV) by Houghton, M., et al., European Patent Application publication number 0 318 216, May 31, 1989. Related papers describing this virus include Kuo, G., et al., Science, 244:359-361 (1989) and Choo, Q., et al., Science, 244:362-364 (1989). Houghton, M., et al. reported isolating cDNA sequences from HCV which encode antigens which react immunologically with antibodies present in patients infected with NANBH, thus establishing that HCV is one of the viral agents causing NANBH. The cDNA sequences associated with HCV were isolated from a cDNA library prepared from the RNA obtained from pooled serum from a chimpanzee with chronic HCV infection. The cDNA library contained cDNA sequences of approximate mean size of about 200 base pairs. The cDNA library was screened for encoded epitopes expressed in clones that could bind to antibodies in sera from patients who had previously experienced NANBH.

In the European Patent Application, Houghton, M., et al. also described the preparation of several superoxide dismutase fusion polypeptides (SOD) and the use of these SOD fusion polypeptides to develop an HCV screening assay. The most complex SOD fusion polypeptide described in the European Patent Application, designated c100-3, was described as containing 154 amino acids of human SOD at the aminoterminus, 5 amino acid residues derived from the expression of a synthetic DNA adapter containing a restriction site, EcoRI, 363 amino acids derived from the expression of a cloned HCV cDNA fragment, and 5 carboxyl terminal amino acids derived from an MS2 cloning vector nucleotide sequence. The DNA sequence encoding this polypeptide was transformed into yeast cells using a plasmid. The transformed cells were cultured and expressed a 54,000 molecular weight polypeptide which was purified to about 80% purity by differential extraction.

Other SOD fusion polypeptides designated SOD-$NANB_{5-1-1}$ and SOD-$NANB_{81}$ were expressed in recombinant bacteria. The E.coli fusion polypeptides

were purified by differential extraction and by chromatography using anion and cation exchange columns. The purification procedures were able to produce SOD-NANB$_{5-1-1}$ as about 80% pure and SOD-NAN38, as about 50% pure.

The recombinant SOD fusion polypeptides described by Houghton, M., et al. were coated on microtiter wells or polystyrene beads and used to assay serum samples. Briefly, coated microtiter wells were incubated with a sample in a diluent. After incubation, the microtiter wells were washed and then developed using either a radioactively labelled sheep anti-human antibody or a mouse antihuman IgG-HRP (horseradish peroxidase) conjugate. These assays were used to detect both post acute phase and chronic phase HCV infection.

Due to the preparative methods, assay specificity required adding yeast or E.coli extracts to the samples in order to prevent undesired immunological reactions with any yeast or E.coli antibodies present in samples.

Ortho Diagnostic Systems Inc. have developed a immunoenzyme assay to detect antibodies to HCV antigens. The Ortho assay procedure is a three-stage test for serum/plasma carried out in a microwell coated with the recombinant yeast/hepatitis C virus SOD fusion polypeptide c100-3.

In the first stage, a test specimen is diluted directly in the test well and incubated for a specified length of time. If antibodies to HCV antigens are present in the specimen, antigen-antibody complexes will be formed on the microwell surface. If no antibodies are present, complexes will not be formed and the unbound serum or plasma proteins will be removed in a washing step.

In the second stage, anti-human IgG murine monoclonal antibody horseradish peroxidase conjugate is added to the microwell. The conjugate binds specifically to the antibody portion of the antigen-antibody complexes. If antigen-antibody complexes are not present, the unbound conjugate will also be removed by a washing step.

In the third stage, an enzyme detection system composed of o-phenylenediamine 2HCl (OPD) and hydrogen peroxide is added to the test well. If bound conjugate is present, the OPD will be oxidized, resulting in a colored end product. After formation of the colored end product, dilute sulfuric acid is added to the microwell to stop the color-forming detection reaction.

The intensity of the colored end product is measured with a microwell reader. The assay may be used to screen patient serum and plasma.

It is established that HCV may be transmitted by contaminated blood and blood products. In transfused patients, as many as 10% will suffer from post-transfusion hepatitis. Of these, approximately 90% are the result of infections

diagnosed as HCV. The prevention of transmission of HCV by blood and blood products requires reliable, sensitive and specific diagnosis and prognostic tools to identify HCV carriers as well as contaminated blood and blood products. Thus, there exists a need for an HCV assay which uses reliable and efficient reagents and methods to accurately detect the presence of HCV antibodies in samples.

SUMMARY OF THE INVENTION

The present invention provides an improved assay for detecting the presence of an antibody to an HCV antigen in a sample by contacting the sample with at least one recombinant protein representing a distinct antigenic region of the HCV genome.

Recombinant antigens which are derived from the molecular cloning and expression of synthetic DNA sequences in heterologous hosts are provided. Briefly, synthetic DNA sequences which encode the desired proteins representing distinct antigenic regions of the HCV genome are optimized for expression in E.coli by specific codon selection. Specifically, recombinant proteins representing five distinct antigenic regions of NS1 of the HCV genome are described. The proteins are expressed as chimeric fusions with E.coli CMP-KDO synthetase (CKS) gene. The first protein, expressed by plasmid pHCV-77 (identified as SEQ. ID. NO. 1) represents amino acids 365-579 of the HCV sequence of NS1 and, based on analogy to the genomic organization of other flaviviruses, has been named HCV CKS-NS1S1. Note that the term pHCV-77 will also refer to the fusion protein itself and that pHCV-77' will be the designation for a polypeptide representing the NS1 region from about amino acids 365-579 of the HCV sequence prepared using other recombinant or synthetic methodologies. Other recombinant methodologies would include the preparation of pHCV-77', utilizing different expression systems. The methodology for the preparation of synthetic peptides of HCV is described in U.S. Serial No. 456,162, filed December 22, 1989, and U.S. Serial No. 610,180, filed November 7, 1990, which enjoy common ownership and are incorporated herein by reference. The next protein is expressed by plasmid pHCV-65, identified as SEQ. ID. NO. 2, and represents amino acids 565-731 of the NS1 region of the HCV genome, pHCV-65 has been named HCV CKS-NS1S2 and is expressed by the plasmid pHCV-65. The fusion protein itself will also be referred to as pHCV-65 and pHCV-65' shall be the designation for a polypeptide from the NS-1 region representing from about amino acids 565-731 of the HCV sequence prepared using other recombinant or synthetic methodologies. The next recombinant antigen represents amino acids 717-847 of the NS1 region of the HCV sequence, and is expressed by the plasmid pHCV-78 (identified by SEQ. ID. NO. 3). The fusion protein will be

referred to as pHCV-78 and pHCV-78' shall be the designation for a polypeptide from the NS1 region representing from about amino acids 717-847 of the HCV sequence prepared using other recombinant or synthetic methodologies. It has been designated clone HCV CKS-NS1S3 based on the strategy used in its construction. Figure 44 illustrates the position of pHCV-77, pHCV-65 and pHCV-78 in the NS1 region of the HCV genome. The recombinant antigen produced by pHCV-80 is identified as SEQ. ID. NO. 4 and is designated HCV CKS-NS1S1-NS1S2. The fusion protein is also designated by pHCV-80 and pHCV-80' refers to the polypeptide located in the NS1 region of HCV, representing amino acids 365-731 of the HCV genome prepared using different recombinant methodologies. Figure 45 illustrates the position of pHCV-80 within the HCV genome. HCV CKS-Full Length NS1 is the designation for the recombinant protein pHCV-92 (SEQ. ID. NO. 5). It represents amino acids 365-847 of the HCV genome. The fusion proteins will be referred to as pHCV-92 and pHCV 92' shall be the designation for the polypeptide from the NS1 region representing amino acids 365-847 of the HCV sequence prepared using other recombinant or synthetic methodologies. Figure 46 illustrates the position of pHCV-92 in the HCV genome. These antigens are used in the inventive immunoassays to detect the presence of HCV antibodies in samples.

One assay format according to the invention provides a screening assay for identifying the presence of an antibody that is immunologically reactive with an HCV antigen. Briefly, a fluid sample is incubated with a solid support containing the commonly bound recombinant proteins. Finally, the antibody-antigen complex is detected. In a modification of the screening assay the solid support additionally contains recombinant polypeptide c100-3.

Another assay format provides a confirmatory assay for unequivocally identifying the presence of an antibody that is immunologically reactive with an HCV antigen. The confirmatory assay includes synthetic peptides or recombinant antigens representing the epitopes contained within the NS1 region of the HCV genome, which are the same regions represented by the recombinant proteins described in the screening assay. These are pHCV-77, pHCV-65, pHCV-78, pHCV-80 and pHCV-92. Recombinant proteins used in the confirmatory assay should have a heterologous source of antigen to that used in the primary screening assay (i.e. should not be an E.coli-derived recombinant antigen nor a recombinant antigen composed in part, of CKS sequences). Briefly, specimens repeatedly reactive in the primary screening assay are retested in the confirmatory assay. Aliquots containing identical amounts of specimen are contacted with a synthetic peptide or recombinant antigen individually coated onto a solid support. Finally, the antibody-

antigen complex is detected. The polypeptides or recombinant proteins can be utilized as indicated or combined with other polypeptides and recombinant proteins a described herein and also described in U.S. Serial No. 456,162 entitled "Hepatitis C Assay", filed December 22, 1989, which enjoys common ownership and is incorporated herein by reference.

Another assay format provides a competition assay or neutralization assay directed to the confirmation that positive results are not false by identifying the presence of an antibody that is immunologically reactive with an HCV antigen in a fluid sample where the sample is used to prepare first and second immunologically equivalent aliquots. The first aliquot is contacted with solid support containing a bound polypeptide which contains at least one epitope of an HCV antigen under conditions suitable for complexing with the antibody to form a detectable antibody-polypeptide complex and the second aliquot is first contacted with the same solid support containing bound polypeptide. The preferred recombinant polypeptides include pHCV-77, pHCV-65, pHCV-78, pHCV-80 and pHCV-92.

Another assay format provides an immunodot assay for identifying the presence of an antibody that is immunologically reactive with an HCV antigen by concurrently contacting a sample with recombinant polypeptides each containing distinct epitopes of an HCV antigen under conditions suitable for complexing the antibody with at least one of the polypeptides and detecting the antibodypolypeptide complex by reacting the complex with colorproducing reagents. The preferred recombinant polypeptides employed include those recombinant polypeptides derived from pHCV-77, pHCV-65, pHCV-78, pHCV-80, as well as pHCV-92.

In all of the assays, the sample is preferably diluted before contacting the polypeptide absorbed on a solid support. Samples may be obtained from different biological samples such as whole blood, serum, plasma, cerebral spinal fluid, and lymphocyte or cell culture supernatants. Solid support materials may include cellulose materials, such as paper and nitrocellulose, natural and synthetic polymeric materials, such as polyacrylamide, polystyrene, and cotton, porous gels such as silica gel, agarose, dextran and gelatin, and inorganic materials such as deactivated alumina, magnesium sulfate and glass. Suitable solid support materials may be used in assays in a variety of well known physical configurations, including microtiter wells, test tubes, beads, strips, membranes, and microparticles. A preferred solid support for a non-immunodot assay is a polystyrene bead. A preferred solid support for an immunodot assay is nitrocellulose.

Suitable methods and reagents for detecting an antibody-antigen complex in an assay of the present invention are commercially available or known in the

relevant art. Representative methods may employ detection reagents such as enzymatic, radioisotopic, fluorescent, luminescent, or chemiluminescent reagents. These reagents may be used to prepare hapten-labelled antihapten detection systems according to known procedures, for example, a biotin-labelled antibiotin system may be used to detect an antibody-antigen complex.

The present invention also encompasses assay kits including polypeptides which contain at least one epitope of an HCV antigen bound to a solid support as well as needed sample preparation reagents, wash reagents, detection reagents and signal producing reagents.

Other aspects and advantages of the invention will be apparent to those skilled in the art upon consideration of the following detailed description which provides illustrations of the invention in its presently preferred embodiments.

E.coli strains containing plasmids useful for constructs of the invention have been deposited at the American Type Culture Collection, Rockville, Maryland on August 10, 1990, under the accession Nos. ATCC 68380 (pHCV-23), ATCC 68381 (pHCV-29), ATCC 68382 (pHCV-31), ATCC 68383 (pHCV-34) and on November 6, 1990 for E.coli strains containing plasmids useful for constructs under the accession Nos. ATCC 68458 (pHCV-50), ATCC 68459 (pHCV-57), ATCC 68460 (pHCV-103), ATCC 68461 (pHCV-102), ATCC 68462 (pHCV-51), ATCC 68463 (pHCV-105), ATCC 68464 (pHCV-107), ATCC 68465 (pHCV-104), ATCC 68466 (pHCV-45), ATCC 68467 (pHCV-48),ATCC 68468 (pHCV-49), ATCC 68469 (pHCV-58) and ATCC 68470 (pHCV-101). E. coli strains containing plasmids useful for constructs of the invention have been deposited at the A.T.C.C. on September 26, 1991 under deposit numbers ATCC 68690 (pHCV-77), ATCC 68696 (pHCV-65), ATCC 68689 (pHCV-78), ATCC 68688 (pHCV-80) and ATCC 68695 (pHCV-92).

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 illustrates the HCV genome.

FIGURE 2 illustrates the use of recombinant polypeptides to identify the presence of antibodies in a chimpanzee inoculated with HCV.

FIGURE 3 illustrates the sensitivity and specificity increase in using the screening assay using pHCV-34 and pHCV-31 antigens.

FIGURE 4 illustrates the construction of plasmid pHCV-34.

FIGURE 5 illustrates fusion protein pHCV-34.

FIGURE 6 illustrates the expression of pHCV-34 proteins in E.coli.

FIGURE 7 illustrates the construction of plasmid pHCV-23.

FIGURE 8 illustrates the construction of plasmid pHCV-29.

FIGURE 9 illustrates the construction of plasmid pHCV-31.

FIGURE 10 illustrates the fusion protein pHCV-31.

FIGURE 11 illustrates the expression of pHCV-29 in E.coli.

FIGURE 12 illustrates the expression of pHCV-23 in E.coli.

FIGURE 13 illustrates the expression of pHCV-31 in E.coli.

FIGURE 14 illustrates the increased sensitivity using the screening assay utilizing the pHCV-34.

FIGURE 15 illustrates the increased specificity with the screening assay utilizing pHCV-34 and pHCV-31.

FIGURE 16 illustrates the results in hemodialysis patients using the screening and confirmatory assays.

FIGURE 17 illustrates earlier detection of HCV in a hemodialysis patient using the screening assay.

FIGURE 18 illustrates the results of the screening assay utilizing pHCV-34 and pHCV-31 on samples from individuals with acute NANBH.

FIGURE 19 illustrates the results of the confirmatory assay of the same population group as in Figure 18.

FIGURE 20 illustrates the results of the screening and confirmatory assays on individuals infected with chronic NANBH.

FIGURE 21 illustrates preferred buffers, pH conditions, and spotting concentrations for the HCV immunodot assay.

FIGURE 22 illustrates the results of the HCV immunodot assay.

FIGURE 23 illustrates the fusion protein pHCV-45.

FIGURE 24 illustrates the expression of pHCV-45 in E.coli.

FIGURE 25 illustrates the fusion protein pHCV-48.

FIGURE 26 illustrates the expression of pHCV-48 in E.coli.

FIGURE 27 illustrates the fusion protein pHCV-51.

FIGURE 28 illustrates the expression of pHCV-51 in E.coli.

FIGURE 29 illustrates the fusion protein pHCV-50.

FIGURE 30 illustrates the expression of pHCV-50 in E.coli.

FIGURE 31 illustrates the fusion protein pHCV-49.

FIGURE 32 illustrates the expression of pHCV-49 in E.coli.

FIGURE 33 illustrates an immunoblot of pHCV-23, pHCV-45, pHCV-48, pHCV-51, pHCV-50 and pHCV-49.

FIGURE 34 illustrates the fusion proteins pHCV-24, pHCV-57, pHCV-58.

FIGURE 35 illustrates the expression of pHCV-24, pHCV-57, and pHCV-58

in E.coli.

FIGURE 36 illustrates the fusion protein pHCV-105.

FIGURE 37 illustrates the expression of pHCV-105 in E.coli.

FIGURE 38 illustrates the fusion protein pHCV-103.

FIGURE 39 illustrates the fusion protein pHCV-101.

FIGURE 40 illustrates the fusion protein pHCV-102.

FIGURE 41 illustrates the expression of pHCV-102 in E.coli.

FIGURE 42 illustrates the fusion protein pHCV-107.

FIGURE 43 illustrates the fusion protein pHCV-104.

FIGURE 44 illustrates the NS1 region of the HCV genome, and in particular, the locations of pHCV-77, pHCV-65 and pHCV-78.

FIGURE 45 illustrates the NS1 region of the HCV genome, and in particular, the location of pHCV-80.

FIGURE 46 illustrates the NS1 region of the HCV genome, and in particlar, the location of pHCV-92.

FIGURE 47A ilustrates the expression of pHCV-77 in E. coli; and FIGURE 47B illustrates an immunblot of pHCV-77 in E. coli.

FIGURE 48A illustrates the expression of pHCV-65 in E. coli and FIGURE 48B illustrates an immunoblot of pHCV-65 in E. coli.

FIGURE 49A illustrates the expression of pHCV-80 in E. coli and FIGURE 49B illustrates an immunoblot of pHCV-80 in E. coli.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to an assay to detect an antibody to an HCV antigen in a sample. Human serum or plasma is preferably diluted in a sample diluent and incubated with a polystyrene bead coated with a recombinant polypeptide that represents a distinct antigenic region of the HCV genome. If antibodies are present in the sample they will form a complex with the antigenic polypeptide and become affixed to the polystyrene bead. After the complex has formed, unbound materials and reagents are removed by washing the bead and the bead-antigen--antibody complex is reacted with a solution containing horseradish peroxidase labeled goat antibodies directed against human antibodies. This peroxidase enzyme then binds to the antigen-antibody complex already fixed to the bead. In a final reaction the horseradish peroxidase is contacted with o-phenylenediamine and hydrogen peroxide which results in a yellow-orange color. The intensity of the color is proportional to the amount of antibody which initially binds to the antigen fixed to the bead.

The preferred recombinant polypeptides having HCV antigenic epitopes were selected from portions of the HCV genome which encoded polypeptides which possessed amino acid sequences similar to other known immunologically reactive agents and which were identified as having some immunological reactivity. (The immunological reactivity of a polypeptide was initially identified by reacting the cellular extract of E.coli clones which had been transformed with cDNA fragments of the HCV genome with HCV infected serum. Polypeptides expressed by clone containing the incorporated cDNA were immunologically reactive with serum known to contain antibody to HCV antigens.) An analysis of a given amino acid sequence, however, only provides rough guides to predicting immunological reactivity. There is no invariably predictable way to ensure immunological activity short of preparing a given amino acid sequence and testing the suspected sequence in an assay.

The use of recombinant polypeptides representing distinct antigenic regions of the HCV genome to detect the presence of an antibody to an HCV antigen is illustrated in Figure 2. The course of HCV infection in the chimpanzee, Pan, was followed with one assay using recombinant c100-3 polypeptide and with another improved assay, using the two recombinant antigens CKS-Core (pHCV-34) (SEQ.ID.NO 6 and 7) and pHCV-33c-BCD (pHCV-31) (SEQ.ID.NO 8 and 9) expressed by the plasmids pHCV-34 and pHCV-31, respectively. The assay utilizing the recombinant pHCV-34 and pHCV-31 proteins detected plasma antibody three weeks prior to detection of antibody by the assay using c100-3.

A summary of the results of a study which followed the course of HCV infection in Pan and six other chimpanzees using the two assays described above is summarized in Figure 3. Both assays gave negative results before inoculation and both assays detected the presence of antibodies after the animal had been infected with HCV. However, in the comparison of the two assays, the improved screening assay using pHCV-34 and pHCV-31 detected seroconversion to HCV antigens at an earlier or equivalent bleed date in six of the seven chimpanzees. Data from these chimpanzee studies clearly demonstrate that overall detection of HCV antibodies is greatly increased with the assay utilizing the pHCV-34 and pHCV-31 proteins. This test is sufficiently sensitive to detect seroconversion during the acute phase of this disease, as defined as an elevation in ALT levels, in most animals. Equally important is the high degree of specificity of the test as no pre-inoculation specimens were reactive.

The polypeptides useful in the practice of this invention are produced using recombinant technologies. The DNA sequences which encode the desired polypeptides

are preferably assembled from fragments of the total desired sequence. Synthetic DNA fragments of the HCV genome can be synthesized based on their corresponding amino acid sequences. Once the amino acid sequence is chosen, this is then reverse translated to determine the complementary DNA sequence using codons optimized to facilitate expression in the chosen system. The fragments are generally prepared using well known automated processes and apparatus. After the complete sequence has been prepared the desired sequence is incorporated into an expression vector which is transformed into a host cell. The DNA sequence is then expressed by the host cell to give the desired polypeptide which is harvested from the host cell or from the medium in which the host cell is cultured. When smaller peptides are to be made using recombinant technologies it may be advantageous to prepare a single DNA sequence which encodes several copies of the desired polypeptide in a connected chain. The long chain is then isolated and the chain is cleaved into the shorter, desired sequences.

The methodology of polymerase chain reaction (PCR) may also be employed to develop PCR amplified genes from any portion of the HCV genome, which in turn may then be cloned and expressed in a manner similar to the synthetic genes.

Vector systems which can be used include plant, bacterial, yeast, insect, and mammalian expression systems. It is preferred that the codons are optimized for expression in the system used.

A preferred expression system utilizes a carrier gene for a fusion system where the recombinant HCV proteins are expressed as a fusion protein of an E.coli enzyme, CKS (CTP:CMP-3-deoxy-manno-octulosonate cytidylyl transferase or CMP-KDO synthetase). The CKS method of protein synthesis is disclosed in U.S. Patent Applications Serial Nos. 167,067 and 276,263 filed March 11, 1988 and November 23, 1988, respectively, by Bolling (EPO 891029282) which enjoy common ownership and are incorporated herein by reference.

Other expression systems may be utilized including the lambda PL vector system whose features include a strong lambda pL promoter, a strong three-frame translation terminator rrnBtl, and translation starting at an ATG codon.

In the present invention, the amino acid sequences encoding for the recombinant HCV antigens of interest were reverse translated using codons optimized to facilitate high level expression in E.coli. Individual oligonucleotides were synthesized by the method of oligonucleotide directed double-stranded break repair disclosed in U.S. Patent Application Serial No. 883,242, filed July 8, 1986 by Mandecki (EPO 87109357.1) which enjoys common ownership and is incorporated herein by reference. Alternatively, the individual oligonucleotides

may be synthesized on the Applied Biosystem 380A DNA synthesizer using methods and reagents recommended by the manufacturer. The DNA sequences of the individual oligonucleotides were confirmed using the Sanger dideoxy chain termination method (Sanger et al., J. Mole. Biol., 162:729 (1982)). These individual gene fragments were then annealed and ligated together and cloned as EcoRI-BamHI subfragments in the CKS fusion vector pJO200. After subsequent DNA sequence confirmation by the Sanger dideoxy chain termination method, the subfragments were digested with appropriate restriction enzymes, gel purified, ligated and cloned again as an EcoRI-BamHI fragment in the CKS fusion vector pJO2OO. The resulting clones were mapped to identify a hybrid gene consisting of the EcoRI-BamHI HCV fragment inserted at the 3' end of the CKS (CMP-KDO synthetase) gene. The resultant fusion proteins, under control of the lac promoter, consist of 239 amino acids of the CKS protein fused to the various regions of HCV.

The synthesis, cloning, and characterization of the recombinant polypeptides as well as the preferred formats for assays using these polypeptides are provided in the following examples. Examples 1 and 2 describe the synthesis and cloning of CKS-Core and CKS-33-BCD, respectively. Example 3 describes a screening assay. Example 4 describes a confirmatory assay. Example 5 describes a competition assay. Example 6 describes an immunodot assay. Example 7 describes the synthesis and cloning of HCV CKS-NS5E, CKS-NS5F, CKS-NS5G, CKS-NS5H and CKS-NS5I. Example 8 describes the preparation of HCV CKS-C100 vectors. Example 9 describes the preparation of HCV PCR derived expression vectors. Example 10 describes the synthesis and characterization of pHCV-77 of NS1. Example 11 describes the synthesis and characterization of pHCV-65 of NS1. Example 12 describes the synthesis and characterization of pHCV-78 of NS1. Example 13 describes the synthesis and characterization of pHCV-80 of NS1. Example 14 describes the synthesis and characterization of pHCV-92 of NS1.

REAGENTS AND ENZYMES

Media such as Luria-Bertani (LB) and Superbroth II (Dri Form) were obtained from Gibco Laboratories Life Technologies, Inc., Madison Wisconsin. Restriction enzymes, Klenow fragment of DNA polymerase I, T4 DNA ligase, T4 polynucleotide kinase, nucleic acid molecular weight standards, M13 sequencing system, X-gal (5-bromo-4-chloro-3-indonyl-ß-D-galactoside), IPTG (isopropyl-ß-D-thiogalactoside), glycerol, Dithiothreitol, 4-chloro-1-naphthol were purchased from Boehringer Mannheim Biochemicals, Indianapolis, Indiana; or New England Biolabs, Inc., Beverly, Massachusetts; or Bethesda Research

Laboratories Life Technologies, Inc., Gaithersburg, Maryland. Prestained protein molecular weight standards, acrylamide (crystallized, electrophoretic grade >99%); N-N'-Methylene-bis-acrylamide (BIS); N,N,N',N',-Tetramethylethylenediamine (TEMED) and sodium dodecylsulfate (SDS) were purchased from BioRad Laboratories, Richmond, California. Lysozyme and ampicillin were obtained from Sigma Chemical Co., St. Louis, Missouri. Horseradish peroxidase (HRPO) labeled secondary antibodies were obtained from Kirkegaard & Perry Laboratories, Inc., Gaithersburg, Maryland. Seaplaque® agarose (low melting agarose) was purchased from FMC Bioproducts, Rockland, Maine.

T50E10 contained 50mM Tris, pH 8.0, lOmM EDTA; 1X TG contained 100mM Tris, pH 7.5 and 10% glycerol; 2X SDS/PAGE loading buffer consisted of 15% glycerol, 5% SDS, lOOmM Tris base, 1M ß-mercaptoethanol and 0.8% Bromophenol blue dye; TBS container 50 mM Tris, pH 8.0, and 150 mM sodium chloride; Blocking solution consisted of 5% Carnation nonfat dry milk in TBS.

HOST CELL CULTURES, DNA SOURCES AND VECTORS

E.coli JM103 cells, pUC8, pUC18, pUC19 and M13 cloning vectors were purchased from Pharmacia LKB Biotechnology, Inc., Piscataway, New Jersey; Competent Epicurean™ coli stains XL1-Blue and JM109 were purchased from Stratagene Cloning Systems, LaJolla, California. RR1 cells were obtained from Coli Genetic Stock Center, Yale University, New Haven, Connecticut; and E.coli CAG456 cells from Dr. Carol Gross, University of Wisconsin, Madison, Wisconsin. Vector pRK248.clts was obtained from Dr. Donald R. Helinski, University of California, San Diego, California.

GENERAL METHODS

All restriction enzyme digestion were performed according to suppliers' instructions. At least 5 units of enzyme were used per microgram of DNA, and sufficient incubation was allowed to complete digestion of DNA. Standard procedures were used for minicell lysate DNA preparation, phenol-chloroform extraction, ethanol precipitation of DNA, restriction analysis of DNA on agarose, and low melting agarose gel purification of DNA fragments (Maniatis et al., Molecular Cloning. A Laboratory Manual [New York: Cold Spring Harbor, 1982]). Plasmid isolations from E.coli strains used the alkali lysis procedure and cesium chloride-ethidium bromide density gradient method (Maniatis et al., supra). Standard buffers were used for T4 DNA ligase and T4 polynucleotide kinase (Maniatis et al.,

supra).

EXAMPLE 1. CKS-CORE

A. Construction of the Plasmid pJ0200

The cloning vector pJO200 allows the fusion of recombinant proteins to the CKS protein. The plasmid consists of the plasmid pBR322 with a modified lac promoter fused to a KdsB gene fragment (encoding the first 239 of the entire 248 amino acids of the E.coli CMP-KDO synthetase of CKS protein), and a synthetic linker fused to the end of the KdsB gene fragment. The cloning vector pJO200 is a modification of vector pTB210. The synthetic linker includes: multiple restriction sites for insertion of genes; translational stop signals, and the trpA rho-independent transcriptional terminator. The CKS method of protein synthesis as well as CKS vectors including pTB210 are disclosed in U.S. Patent Application Serial Nos. 167,067 and 276,263, filed March 11, 1988 and November 23, 1988, respectively, by Bolling (EPO 891029282) which enjoy common ownership, and are herein incorporated by reference.

B. Preparation of HCV CKS-Core Expression Vector

Six individual nucleotides representing amino acids 1-150 of the HCV genome were ligated together and cloned as a 466 base pair EcoRI-BamHI fragment into the CKS fusion vector pJO200 as presented in Figure 4. The complete DNA sequence of this plasmid, designated pHCV-34, and the entire amino acid sequence of the pHCV-34 recombinant antigen produced is presented in SEQ.ID.NO 6 and 7. The resultant fusion protein HCV CKS-Core, consists of 239 amino acids of CKS, seven amino acids contributed by linker DNA sequences, and the first 150 amino acids of HCV as illustrated in Figure 5.

The pHCV-34 plasmid and the CKS plasmid pTB210 were transformed into E.coli K-12 strain xL-I (recAI, endAI, gyrA96, thi-1, hsdRI7, supE44, relAI, lac/F', proAB, laclqZDM15, TN10) cells made competent by the calcium chloride method. In these constructions the expression of the CKS fusion proteins was under the control of the lac promoter and was induced by the addition of IPTG. These plasmids replicated as independent elements, were nonmobilizable and were maintained at approximately 10-30 copies per cell.

C. Characterization of Recombinant HCV-Core

In order to establish that clone pHCV-34 expressed the unique HCV-CKS Core protein, the pHCV-34/XL-1 culture was grown overnight at 37°C in growth

media consisting of yeast extract, trytone, phosphate salts, glucose, and ampicillin. When the culture reached an OD600 of 1.0, IPTG was added to a final concentration of 1mM to induce expression. Samples (1.5 ml) were removed at 1 hour intervals, and cells were pelleted and resuspended to an OD600 of 1.0 in 2X SDS/PAGE loading buffer. Aliquots (15ul) of the prepared samples were separated on duplicate 12.5% SDS/PAGE gels.

One gel was fixed in a solution of 50% methanol and 10% acetic acid for 20 minutes at room temperature, and then stained with 0.25% Coomassie blue dye in a solution of 50% methanol and 10% acetic acid for 30 minutes. Destaining was carried out using a solution of 10% methanol and 7% acetic acid for 3-4 hours, or until a clear background was obtained.

Figure 6 presents the expression of pHCV-34 proteins in E.coli. Molecular weight standards were run in Lane M. Lane 1 contains the plasmid pJ0200-the CKS vector without the HCV sequence. The arrows on the left indicate the mobilities of the molecular weight markers from top to bottom: 110,000; 84,000; 47,000; 33,000; 24,000; and 16,000 daltons. The arrows on the right indicate the mobilities of the recombinant HCV proteins. Lane 2 contains the E.coli lysate containing pHCV-34 expressing CKS-Core (amino acids 1 to 150) prior to induction; and Lane 3 after 3 hours of induction. The results show that the recombinant protein pHCV-34 has an apparent mobility corresponding to a molecular size of 48,000 daltons. This compares acceptably with the predicted molecular mass of 43,750 daltons.

Proteins from the second 12.5% SDS/PAGE gel were electrophoretically transferred to nitrocellulose for immunoblotting. The nitrocellulose sheet containing the transferred proteins was incubated with Blocking Solution for one hour and incubated overnight at 4°C with HCV patients' sera diluted in TBS containing E.coli K-12 strain XL-I lysate. The nitrocellulose sheet was washed three times in TBS, then incubated with HRPO-labeled goat anti-human IgG, diluted in TBS containing 10% fetal calf sera. The nitrocellulose was washed three times with TBS and the color was developed in TBS containing 2 mg/ml 4-chloro-1-napthol, 0.02% hydrogen peroxide and 17% methanol. Clone HCV-34 demonstrated a strong immunoreactive band at 48,000 daltons with the HCV patients' sera. Thus, the major protein in the Coomassie stained protein gel was immunoreactive. Normal human serum did not react with any component of pHCV-34.

EXAMPLE 2. HCV CKS-33C-BCD

A. Preparation of HCV CKS-33c-BCD Expression Vector

The construction of this recombinant clone expressing the HCV CKS-33-BCD antigen was carried out in three steps described below. First, a clone expressing the HCV CKS-BCD antigen was constructed, designated pHCV-23. Second, a clone expressing the HCV CKS-33 antigen was constructed, designated pHCV-29. Lastly, the HCV BCD region was excised from pHCV-23 and inserted into pHCV-29 to construct a clone expressing the HCV CKS-33-BCD antigen, designated pHCV-31 (SEQ.ID.NO. 8 and 9).

To construct the plasmid pHCV-23, thirteen individual oligonucleotides representing amino acids 1676-1931 of the HCV genome were ligated together and cloned as three separate EcoRI-BamHI subfragments into the CKS fusion vector pJO200. After subsequent DNA sequence confirmation, the three subfragments, designated B, C, and D respectively, were digested with the appropriate restriction enzymes, gel purified, ligated together, and cloned as a 781 base pair EcoRI-BamHI fragment in the CKS fusion vector pJO200, as illustrated in Figure 7. The resulting plasmid, designated pHCV-23, expresses the HCV CKS-BCD antigen under control of the lac promoter. The HCV CKS-BCD antigen consists of 239 amino acids of CKS, seven amino acids contributed by linker DNA sequences, 256 amino acids from the HCV NS4 region (amino acids 1676-1931, and 10 additional amino acids contributed by linker DNA sequences.

To construct the plasmid pHCV-29 twelve individual oligonucleotides representing amino acids 1192-1457 of the HCV genome were ligated together and cloned as two separate EcoRI-BamHI subfragments in the CKS fusion vector pJO200. After subsequent DNA sequence confirmation, the two subfragments were digested with the appropriate restriction enzymes, gel purified, ligated together and cloned again as an 816 base pair EcoRI-BamHI fragment in the CKS fusion vector pJO200, as illustrated in Figure 8. The resulting plasmid, designated pHCV-29, expresses the CKS-33 antigen under control of the lac promoter. The HCV CKS-33 antigen consists of 239 amino acids of CKS, eight amino acids contributed by linker DNA sequences, and 266 amino acids from the HCV NS3 region (amino acids 1192-1457).

To construct the plasmid pHCV-31, the 781 base pair EcoRI-BamHI fragment from pHCV-23 representing the HCV-BCD region was linker-adapted to produce a Cla1-BamH1 fragment which was then gel purified and ligated into pHCV-29 at the Cla1-BamH1 sites as illustrated in Figure 9. The resulting plasmid, designated pHCV-31, expresses the pHCV-31 antigen under control of the lac promoter. The complete DNA sequence of pHCV-31 and the entire amino acid sequence of the HCV CKS-33-BCD recombinant antigen produced is presented in

SEQ.ID.NO. 8 and 9. The HCV CKS-33-BCD antigen consists of 239 amino acids of CKS, eight amino acids contributed by linker DNA sequences, 266 amino acids of the HCV NS3 region (amino acids 1192-1457), 2 amino acids contributed by linker DNA sequences, 256 amino acids of the HCV NS4 region (amino acids 1676-1931), and 10 additional amino acids contributed by linker DNA sequences. Figure 12 presents a schematic representation of the pHCV-31 antigen.

The pHCV-31 plasmid was transformed into E.coli K-12 strain XL-I in a manner similar to the pHCV-34 and CKS-pTB210 plasmids of Example 1.

B. Characterization of Recombinant HCV CKS-33-BCD

Characterization of pHCV CKS-33-BCD was carried out in a manner similar to pHCV CKS-Core of Example 1. pHCV-23, pHCV SDS/PAGE gels were run for E.coli lysates containing the plasmids pHCV-29 (Figure 11), pHCV-23 (Figure 12), and pHCV-31 (Figure 13) expressing the recombinant fusion proteins CKS-33c, CKS-BCD, and CKS-33-BCD, respectively. For all three figures, molecular weight standards were run in Lane M, with the arrows on the left indicating mobilities of the molecular weight markers the from top to bottom: 110,000; 84,000; 47,000; 33,000; 24,000; and 16,000 daltons. In Figure 11, Lane 1 contained the E.coli lysate containing pHCV-29 expressing HCV CKS-33c (amino acids 1192 to 1457) prior to induction and lane 2 after 4 hours induction. These results show that the recombinant pHCV-29 fusion protein has an apparent mobility corresponding to a molecular size of 60,000 daltons. This compares acceptably to the predicted molecular mass of 54,911.

In Figure 12, Lane 1 contained the E.coli lysate containing pJO200-- the CKS vector without the HCV sequence. Lane 2, contained pHCV-20 expressing the HCV CKS-B (amino acids 1676 to 1790). Lane 3, contained the fusion protein pHCV-23 (amino acids 1676-1931). These results show that the recombinant pHCV-23 fusion protein has an apparent mobility corresponding to a molecular size of 55,000 daltons. This compares acceptably to the predicted molecular mass of 55,070 daltons.

In Figure 13, Lane 1 contained the E.coli lysate containing pJO200 the CKS vector without the HCV sequences. Lane 2 contained pHCV-31 expressing the CKS-33c-BCD fusion protein (amino acids 1192 to 1447 and 1676 to 1931) prior to induction and lane 3 after 2 hours induction. These results show that the recombinant pHCV-31 (CKS-33c-BCD) fusion protein has an apparent mobility corresponding to a molecular size of 90,000 daltons. This compares acceptably to the predicted molecular mass of 82,995 daltons.

An immunoblot was also run on one of the SDS/PAGE gels derived from the pHCV-31/X1-1 culture. Human serum from an HCV exposed individual reacted strongly with the major pHCV-31 band at 90,000 daltons. Normal human serum did not react with any component of the pHCV-31 (CKS-33-BCD) preparations.

EXAMPLE 3. SCREENING ASSAY

The use of recombinant polypeptides which contain epitopes within c100-3 as well as epitopes from other antigenic regions from the HCV genome, provide immunological assays which have increased sensitivity and may be more specific than HCV immunological assays using epitopes within c100-3 alone.

In the presently preferred screening assay, the procedure uses two E.coli expressed recombinant proteins, CKS-Core (pHCV-34) and CKS-33-BCD (pHCV-31), representing three distinct regions of the HCV genome. These recombinant polypeptides were prepared following procedures described above. In the screening assay, both recombinant antigens are coated onto the same polystyrene bead. In a modification of the screening assay the polystyrene bead may also be coated with the SOD-fusion polypeptide c100-3.

The polystyrene beads are first washed with distilled water and propanol and then incubated with a solution containing recombinant pHCV-31 diluted to 0.5 to 2.0 ug/ml and pHCV-34 diluted to 0.1 to 0.5 ug/ml in 0.1 M NaH_2PO_4-H_20 with 0.4M NaC1 and 0.0022% Triton X-100, pH 6.5. The beads are incubated in the antigen solution for 2 hours (plus or minus 10 minutes) at 38-42°C, washed in PBS and soaked in 0.1% (w/v) Triton X-100 in PBS for 60 minutes at 38-42°C. The beads are then washed two times in phosphate buffered saline (PBS), overcoated with a solution of 5.0% (w/v) bovine serum albumin (BSA) in PBS for 60 minutes at 38-42°C and washed one time in PBS. Finally, the beads are overcoated with 5% (w/v) sucrose in PBS, and dried under nitrogen or air.

The polystyrene beads coated with pHCV-31 and pHCV-34 are used in an antibody capture format. Ten microliters of sample are added to the wells of the reaction tray along with 400 ul of a sample diluent and the recombinant coated bead. The sample diluent consists of 10% (v/v) bovine serum and 20% (v/v) goat serum in 20 mM Tris phosphate buffer containing 0.15% (v/v) Triton X-100, 1%(w/v) BSA, 1% E.coli lysate and 500 ug/ml or less CKS lysate. When the recombinant yeast c100-3 polypeptide is used, antibodies to yeast antigens which may be present in a sample are reacted with yeast extracts which are added to the sample diluent (typically about 200 ug/ml). The addition of yeast extracts to the sample diluent is used to prevent false positive results. The final material is sterile

filtered and filled in plastic bottles, and preserved with 0.1% sodium azide.

After one hour of incubation at 40°C, the beads are washed and 200 ul of conjugate is added to the wells of the reaction tray.

The preferred conjugate is goat anti-human IgG horseradish peroxidase conjugate. Concentrated conjugate is titered to determine a working concentration. A twenty-fold concentrate of the working conjugate solution is then prepared by diluting the concentrate in diluent. The 20X concentrate is sterile filtered and stored in plastic bottles.

The conjugate diluent includes 10% (v/v) bovine serum, 10% (v/v) goat serum and 0.15% Triton-X100 in 20 mM Tris buffer, pH 7.5 with 0.01% gentamicin sulfate, 0.01% thimerosal and red dye. The conjugate is sterile filtered and filled in plastic bottles.

Anti-HCV positive control is prepared from plasma units positive for antibodies to HCV. The pool of units used includes plasma with antibodies reactive to pHCV-31 and pHCV-34. The units are recalcified and heat inactivated at 59-61°C for 12 hours with constant stirring. The pool is aliquoted and stored at -20°C or at 2-8°C. For each lot of positive control, the stock solution is diluted with negative control containing 0.1% sodium azide as a preservative. The final material is sterile filtered and filled in plastic bottles.

Anti-HCV negative control is prepared from recalcified human plasma, negative for antibodies to pHCV-31 and pHCV-34 proteins of HCV. The plasma is also negative for antibodies to human immunodeficiency virus (HIV) and negative for hepatitis B surface antigen (HBsAg). The units are pooled, and 0.1% sodium azide is added as a preservative. The final material is sterile filtered and filled in plastic bottles.

After one hour of incubation with the conjugate at 40°C, the beads are washed, exposed to the OPD substrate for thirty minutes at room temperature and the reaction terminated by the addition of 1 N H_2SO_4. The absorbance is read at 492 nm.

In order to maintain acceptable specificity, the cutoff for the assay should be at least 5-7 standard deviations above the absorbance value of the normal population mean. In addition, it has generally been observed that acceptable specificity is obtained when the population mean runs at a sample to cutoff (S/CO) value of 0.25 or less. Consistent with these criteria, a "preclinical" cutoff for the screening assay was selected which clearly separated most of the presumed "true negative" from "true positive" specimens. The cutoff value was calculated as the sum of the positive control mean absorbance value multiplied by 0.25 and the

negative control mean absorbance value. The cutoff may be expressed algebraically as:

Cutoff value=0.25 PCx + NCx.

Testing may be performed by two methods which differ primarily in the degree of automation and the mechanism for reading the resulting color development in the assay. One method is referred to as the manual or Quantum™ method because Quantum or Quantumatic is used to read absorbance at 492 nm. It is also called the manual method because sample pipetting, washing and reagent additions are generally done manually by the technician, using appropriately calibrated pipettes, dispensers and wash instruments. The second method is referred to as the PPC method and utilizes the automated Abbott Commander® system. This system employs a pipetting device referred to as the Sample Management Center (SMC) and a wash/dispense/read device referred to as the Parallel Processing Center (PPC) disclosed in E.P.O. Publication No. 91114072.1. The optical reader used in the PPC has dual wavelength capabilities that can measure differential absorbencies (peak band and side band) from the sample wells. These readings are converted into results by the processor's Control Center.

Screening Assay Performance

1. Serum/Plasma From Inoculated Chimpanzees

As previously described, Table I summarizes the results of a study which followed the course of HCV infection in seven chimpanzees using a screening assay which utilized the c100-3 polypeptide, and the screening assay which utilized pHCV-31 and pHCV-34. Both assays gave negative results before inoculation and both assays detected the presence of antibodies after the animal had been infected with HCV. However, in the comparison of the two assays, the assay utilizing pHCV-31 and pHCV-34 detected seroconversion to HCV antigens at an earlier or equivalent bleed date in six of the seven chimpanzees. Data from these chimpanzee studies clearly demonstrate that overall detection of HCV antibodies is greatly increased with the assay utilizing the pHCV-31 and pHCV-34 proteins. This test is sufficiently sensitive to detect seroconversion during the acute phase of this disease, as defined as an elevation in ALT levels, in most animals. Equally important is the high degree of specificity of the test as no pre-inoculation specimens were reactive.

2. Non-A, Non-B Panel II (H. Alter, NIH)

A panel of highly pedigreed human sera from Dr. H. Alter, NIH, Bethesda,

MD., containing infectious HCV sera, negative sera and other disease controls were tested. A total of 44 specimens were present in the panel.

Six of seven sera which were "proven infectious" in chimpanzees were positive in both the screening assay using c100-3 as well as in the screening assay utilizing the recombinant proteins pHCV-31 and pHCV-34. These six reactive specimens were obtained from individuals with chronic hepatitis. All six of the reactive specimens were confirmed positive using synthetic peptide sp67. One specimen obtained during the acute phase of NANB post-transfusion hepatitis was non-reactive in both screening assays.

In the group labeled "probable infectious" were three samples taken from the same post transfusion hepatitis patient. The first two acute phase samples were negative in both assays, but the third sample was reactive in both assay. The disease control samples and pedigreed negative controls were uniformly negative.

All sixteen specimens detected as positive by both screening assays were confirmed by the spII7 confirmatory assay (Figure 14). In addition, specimens 10 and 29 were newly detected in the screening assay utilizing the recombinant pHCV-31 and pHCV-34 antigens and were reactive by the sp75 confirmatory assay. Specimen 39 was initially reactive in the screening test utilizing pHCV-34 and pHCV-31, but upon retesting was negative and could not be confirmed by the confirmatory assays.

In summary, both screening tests identified 6 of 6 chronic NANBH carriers and 1 of 4 acute NANBH samples. Paired specimens from an implicated donor were non-reactive in the screening test utilizing c100-3 but were reactive in the screening test with pHCV-31 and pHCV-34. Thus, the screening test utilizing the recombinant antigens pHCV-31 and pHCV-34 appears to be more sensitive than the screening assay utilizing c100-3. None of the disease control specimens or pedigreed negative control specimens were reactive in either screening assay.

3. CBER Reference Panel

A reference panel for antibody to Hepatitis C was received from the Center for Biologics Evaluation and Research (CBER). This 10 member panel consists of eight reactive samples diluted in normal human sera negative for antibody to HCV and two sera that contain no detectable antibody to HCV. This panel was run on the Ortho first generation HCV EIA assay, the screening assay utilizing c100-3 and the screening assay utilizing pHCV-31 and pHCV-34. The assay results are presented in Figure 15.

The screening assay utilizing pHCV-31 and pHCV-34 detected all six of the

HCV positive or borderline sample dilutions. The two non-reactive sample dilutions (709 and 710) appear to be diluted well beyond endpoint of antibody detectability for both screening assays. A marked increase was observed in the sample to cutoff values for three of the members on the screening assay utilizing pHCV-31 and pHCV-34 compared to the screening assay utilizing c100-3 or the Ortho first generation test. All repeatably reactive specimens were confirmed.

EXAMPLE 4. CONFIRMATORY ASSAY

The confirmatory assay provides a means for unequivocally identifying the presence of an antibody that is immunologically reactive with an HCV antigen. The confirmatory assay includes synthetic peptides or recombinant antigens representing major epitopes contained within the three distinct regions of the HCV genome, which are the same regions represented by the two recombinant antigens described in the screening assay. Recombinant proteins used in the confirmatory assay should have a heterologous source of antigen to that used in the primary screening assay (i.e. should not be an E.coli-derived recombinant antigen nor a recombinant antigen composed in part, of CKS sequences). Specimens repeatedly reactive in the primary screening assay are retested in the confirmatory assay. Aliquots containing identical amounts of specimen are contacted with a synthetic peptide or recombinant antigen individually coated onto a polystyrene bead. Seroreactivity for epitopes within the c100-3 region of the HCV genome are confirmed by use of the synthetic peptides sp67 and sp65. The synthetic peptide sp117 can also be used to confirm seroreactivity with the c100-3 region. Seroreactivity for HCV epitopes within the putative core region of HCV are confirmed by the use of the synthetic peptide sp75. In order to confirm seroreactivity for HCV epitopes within the 33c region of HCV, a recombinant antigen expressed as a chimeric protein with superoxide dismutase (SOD) in yeast is used. Finally, the antibody-antigen complex is detected.

The assay protocols were similar to those described in Example 3 above. The peptides are each individually coated onto polystyrene beads and used in an antibody capture format similar to that described for the screening assay. Ten microliters of specimen are added to the wells of a reaction tray along with 400 ul of a specimen diluent and a peptide coated bead. After one hour of incubation at 40°C, the beads are washed and 200 ul of conjugate (identical to that described in Example 3) is added to the wells of the reaction tray. After one hour of incubation at 40°C, the beads are washed, exposed to the OPD substrate for 30 minutes at room temperature and the reaction terminated by the addition of 1 N H_2SO_4. The absorbance is read at

492 nm. The cutoff value for the peptide assay is 4 times the mean of the negative control absorbance value.

1. Panels containing Specimens "At Risk" for HCV Infection.

A group of 233 specimens representing 23 hemodialysis patients all with clinically diagnosed NANBH were supplied by Gary Gitnick, M.D. at the University of California, Los Angeles Center for the Health Sciences. These samples which were tested in by the screening assay utilizing c100-3 were subsequently tested in the screening assay which uses pHCV-31 and pHCV-34. A total of 7/23 patients (30.44%) were reactive in the c100-3 screening assay, with a total of 36 repeat reactive specimens. Ten of 23 patients (43.48%) were reactive by the screening assay utilizing pHCV-31 and pHCV-34, with a total of 70 repeatable reactives among the available specimens (Figure 16). Two specimens were unavailable for testing. All of the 36 repeatedly reactive specimens detected in the c100-3 screening assay were confirmed by synthetic peptide confirmatory assays. A total of 34 of these 36 were repeatedly reactive on HCV EIA utilizing pHCV-34 and pHCV-31; two specimens were not available for testing. Of the 36 specimens additionally detected by the screening assay utilizing pHCV-34 and pHCV-31, 9 were confirmed by the core peptide confirmatory assay (sp75) and 27 were confirmed by the SOD-33c confirmatory assay.

In summary these data indicate that detection of anti-HCV by the screening assay utilizing pHCV-31 and pHCV-34 may occur at an equivalent bleed date or as many as 9 months earlier, when compared to the c100-3 screening assay. Figure 17 depicts earlier detection by the screening assay utilizing pHCV-34 and pHCV-31 in a hemodialysis patient.

5. Acute/Chronic Non-A, Non-B Hepatitis

A population of specimens was identified from individuals diagnosed as having acute or chronic NANBH. Specimens from individuals with acute cases of NANBH were received from Gary Gitnick, M.D. at the University of California, Los Angeles Center for Health Sciences. The diagnosis of acute hepatitis was based on the presence of a cytolytic syndrome (ALT levels greater than 2X the upper normal limit) on at least 2 serum samples for a duration of less than 6 months with or without other biological abnormalities and clinical symptoms. All specimens were also negative for IgM antibodies to Hepatitis A Virus (HAV) and were negative for Hepatitis B surface Ag when tested with commercially available tests. Specimens from cases of chronic NANBH were obtained from two clinical sites. Individuals

were diagnosed as having chronic NANBH based on the following criteria: persistently elevated ALT levels, liver biopsy results, and/or the absence of detectable HBsAg. Specimens with biopsy results were further categorized as either chronic active NANBH, chronic persistent NANBH, or chronic NANBH with cirrhosis.

These specimens were tested by both the c100-3 screening assay and the screening assay utilizing pHCV-34 and pHCV-31. The latter testing was performed in replicates of two by both the Quantum and PPC methods.

Community Acquired NANBH (Acute)

The c100-3 screening assay detected 2 of 10 specimens (20.00%) as repeatedly reactive, both of which were confirmed. The screening assay utilizing pHCV-34 and pHCV-31 detected both of these specimens plus and additional 2 specimens (Figure 18). These 2 specimens were confirmed by sp75 (see Figure 19).

Acute Post-Transfusion NANBH

The c100-3 assay detected 4 of 32 specimens (12.50%) as repeatedly reactive, all of which was confirmed. The screening assay utilizing pHCV-34 and pHCV-31 detected 3 out of these 4 specimens (75%) as reactive. The one sample that was missed had an S/CO of 0.95 by the latter screening test. This sample was confirmed by the sp67 peptide (Figure 18). In addition, the screening assay utilizing pHCV-34 and pHCV-31 detected 11 specimens not reactive in the c100-3 screening assay. Of the 9 specimens available for confirmation, 8 were confirmed by sp75 and 1 could not be confirmed but had an S/CO of 0.90 in the sp65 confirmatory test. (see Figure 19).

Chronic NANBH

A summary of the results on these populations is shown in Figure 20. Overall, 155 of 164 (94.5%) chronic NANBH samples were detected by the screening test utilizing pHCV-31 and pHCV-34 using either Quantum or PPC. The 155 reactive samples were all confirmed in alternate assays using synthetic peptides based on sequences from either the cl00, 33c or core regions of the HCV genome. In contrast, only 138 of 164 (84.1%) specimens were positive by the cl00-3 assay. All but one of the 138 c100-3 samples were detected as positive by the screening assay utilizing pHCV-31 and pHCV-34. The one discordant specimen was not confirmed by either synthetic or neutralization assays. Conversely, there were 17 confirmed specimens which were positive only by the screening assay utilizing pHCV-34 and pHCV-31.

The results indicate that the screening assay utilizing pHCV-34 and pHCV-

31 is more sensitive than the current test in detecting HCV positive individuals within chronically infected NANBH populations.

EXAMPLE 5. Competition ASSAY

The recombinant polypeptides containing antigenic HCV epitopes are useful for competition assays. To perform a neutralization assay, a recombinant polypeptide representing epitopes within the c100-3 region such as CKS-BCD (pHCV-23) is solubilized and mixed with a sample diluent to a final concentration of 0.5-50 ug/ml. Ten microliters of specimen or diluted specimen is added to a reaction well followed by 400 ul of the sample diluent containing the recombinant polypeptide and if desired, the mixture may be preincubated for about fifteen minutes to two hours. A bead coated with c100-3 antigen is then added to the reaction well and incubated for one hour at 40°C. After washing, 200 ul of a peroxidase labeled goat anti-human IgG in conjugate diluent is added and incubated for one hour at 40°C. After washing, OPD substrate is added and incubated at room temperature for thirty minutes. The reaction is terminated by the addition of 1 N sulfuric acid and the absorbance read at 492 nm.

Samples containing antibodies to the c100-3 antigen generate a reduced signal caused by the competitive binding of the peptides to these antibodies in solution. The percentage of competitive binding may be calculated by comparing the absorbance value of the sample in the presence of a recombinant polypeptide to the absorbance value of the sample assayed in the absence of a recombinant polypeptide at the same dilution.

EXAMPLE 6. IMMUNODOT ASSAY

The immunodot assay system uses a panel of purified recombinant polypeptides placed in an array on a nitrocellulose solid support. The prepared solid support is contacted with a sample and captures specific antibodies to HCV antigens. The captured antibodies are detected by a conjugate-specific reaction. Preferably, the conjugate specific reaction is quantified using a reflectance optics assembly within an instrument which has been described in U.S. Patent Applications Serial No. 07/227,408 filed August 2, 1988. The related U.S. Patent Applications Serial Nos. 07/227,272, 07/227,586 and 07/227,590 further describe specific methods and apparatus useful to perform an immunodot assay. The assay has also been described in U.S. Application Serial No. 07/532,489 filed June 6, 1990. Briefly, a nitrocellulose-base test cartridge is treated with multiple antigenic polypeptides. Each polypeptide is contained within a specific reaction zone on the

test cartridge. After all the antigenic polypeptides have been placed on the nitrocellulose, excess binding sites on the nitrocellulose are blocked. The test cartridge is then contacted with a sample such that each antigenic polypeptide in each reaction zone will react if the sample contains the appropriate antibody. After reaction, the test cartridge is washed and any antigen-antibody reactions are identified using suitable well known reagents.

As described in the patent applications listed above, the entire process is amenable to automation. The specifications of these applications related to the method and apparatus for performing an immunodot assay are incorporated by reference herein.

In a preferred immunodot assay, the recombinant polypeptides pHCV-23, pHCV-29, pHCV-34, and c100-3 were diluted in the preferred buffers, pH conditions, and spotting concentrations as summarized in Figure 21 and applied to a preassembled nitrocellulose test cartridge. After drying the cartridge overnight at room temperature 37°C, the non-specific binding capacity of the nitro-cellulose phase was blocked. The blocking solution contained 1% porcine gelatin, 1% casein enzymatic hydrolysate, 5% Tween-20, 0.1% sodium azide, 0.5 M sodium chloride and 20 mM Tris, pH 7.5.

Forty normal donors were assayed by following the method described above. The mean reflectance density value then was determined for each of the recombinant proteins. A cutoff value was calculated as the negative mean plus six standard deviations. Test cartridges were incubated with samples A00642 and 423 (see Figure 22). Sample A00642 was from a convalescent non-A, non-B hepatitis patient, diluted in negative human plasma from 1:100 to 1:12800. The other sample, 423, was from a paid plasma donor which tested positive in an assay using a recombinant c100-3 polypeptide, diluted in negative human plasma from 1:40 to 1:2560. After sample incubation, sequential incubations with a biotin-conjugated goat anti-human immunoglobulin-specific antibody, an alkaline phosphatase-conjugated rabbit anti-biotin specific antibody, and 5-bromo-4-chloro-3-indolyl phosphate produced a colored product at the site of the reaction. Sample to cutoff values (S/CO) were determined for all HCV recombinant proteins. Those S/CO values greater than or equal to 1.0 were considered reactive. The limiting dilution was defined as the lowest dilution at which the S/CO was greater than or equal to 1.0. As seen in Figure 22, each sample tested positive for all HCV recombinant proteins. The data demonstrate that reactivity for sample A00642 was greatest with pHCV-29, and decreased for the remaining antigens pHCV-23, c100-3, and pHCV-34. Sample 423 most strongly reacted with the recombinant proteins

expressing pHCV-29 and pHCV-34, and to a lesser extent with pHCV-23 and c100-3.

EXAMPLE 7. HCV CKS-NS5 EXPRESSION VECTORS

A. Preparation of HCV CKS-NS5E

Eight individual oligonucleotides representing amino acids 1932-2191 of the HCV genome were ligated together and cloned as a 793 base pair EcoRI-BamHI fragment into the CKS fusion vector pJ0200. The resulting plasmid, designated pHCV-45 (SEQ.ID.NO 8), expresses the HCV CKS-NS5E antigen under control of the lac promoter. The HCV CKS-NS5E antigen consists of 239 amino acids of CKS, nine amino acids contributed by linker DNA sequences, and 260 amino acids from the HCV NS4/NS5 region (amino acids 1932-2191). Figure 23 presents a schematic representation of the recombinant antigen expressed by pHCV-45. SEQ.ID.NO. 10 and 11 presents the DNA and amino acid sequence of the HCV CKS-NS5E recombinant antigen produced by pHCV-45. Figure 24 presents the expression of pHCV-45 proteins in E.coli. Lane 1 contained the E.coli lysate containing pHCV-45 expressing the HCV CKS-NS5E antigen (amino acids 1932-2191) prior to induction and lanes 2 and 3 after 2 and 4 hours post induction, respectively. These results show that the pHCV-45 fusion protein has an apparent mobility corresponding to a molecular size of 55,000 daltons. This compares acceptably to the predicted molecular mass of 57,597 daltons.

B. Preparation of HCV CKS-NS5F

Eleven individual oligonucleotides representing amino acids 2188-2481 of the HCV genome were ligated together and cloned as a 895 base pair EcoRI-BamHI fragment into the CKS fusion vector pJ0200. The resulting plasmid, designated pHCV-48 , expresses the HCV CKS-NS5F antigen under control of the lac promoter. The HCV CKS-NS5F antigen consists of 239 amino acids of CKS, eight amino acids contributed by linker DNA sequences, and 294 amino acids from the HCV NS5 region (amino acids 2188-2481). Figure 25 presents a schematic representation of the recombinant antigen expressed by pHCV-48. SEQ.ID.NO. 12 and 13 presents the DNA and amino acid sequence of the HCV CKS-NS5F recombinant antigen produced by pHCV-48. Figure 26 presents the expression of pHCV-48 proteins in E.coli. Lane 1 contained the E.coli lysate containing pHCV-48 expressing the HCV CKS-NS5F antigen (amino acids 2188-2481) prior to induction and lanes 2 and 3 after 2 and 4 hours post induction, respectively. These results show that the pHCV-48 fusion protein has an apparent mobility corresponding to a molecular size of 65,000

daltons. This compares acceptably to the predicted molecular mass of 58,985 daltons.

C. Preparation of HCV CKS-NS5G

Seven individual oligonucleotides representing amino acids 2480-2729 of the HCV genome were ligated together and cloned as a 769 base pair EcoRI-BamHI fragment into the CKS fusion vector pJ0200. The resulting plasmid, designated pHCV-51 (SEQ.ID.NO. 10), expresses the HCV CKS-NS5G antigen under control of the lac promoter. The HCV CKS-NS5G antigen consists of 239 amino acids of CKS, eight amino acids contributed by linker DNA sequences, and 250 amino acids from the HCV NS5 region (amino acids 2480-2729). Figure 27 presents a schematic representation of the recombinant antigen expressed by pHCV-51. SEQ.NO.ID NO.14 and 15 presents the DNA and amino acid sequence of the HCV CKS-NS5G recombinant antigen produced by pHCV-51. Figure 28 presents the expression of pHCV-51 proteins in E.coli. Lane 1 contained the E.coli lysate containing pHCV-51 expressing the HCV CKS-NS5G antigen (amino acids 2480-2729) prior to induction and lanes 2 and 3 after 2 and 4 hours post induction, respectively. These results show that the pHCV-51 fusion protein has an apparent mobility corresponding to a molecular size of 55,000 daltons. This compares acceptably to the predicted molecular mass of 54,720 daltons.

D. Preparation of HCV CKS-NS5H

Six individual oligonucleotides representing amino acids 2728-2867 of the HCV genome were ligated together and cloned as a 439 base pair EcoRI-BamHI fragment into the CKS fusion vector pJ0200. The resulting plasmid, designated pHCV-50 (SEQ.NO.ID.11) expresses the HCV CKS-NS5H antigen under control of the lac promoter. The HCV CKS-NS5H antigen consists of 239 amino acids of CKS, eight amino acids contributed by linker DNA sequences, and 140 amino acids from the HCV NS5 region (amino acids 2728-2867). Figure 29 presents a schematic representation of the recombinant antigen expressed by pHCV-50. SEQ.ID.NO. 16 and 17 presents the DNA and amino acid sequence of the HCV CKS-NS5H recombinant antigen produced by pHCV-50. Figure 30 presents the expression of pHCV-50 proteins in E.coli. Lane 1 contained the E.coli lysate containing pHCV-50 expressing the HCV CKS-NS5H antigen (amino acids 2728-2867) prior to induction and lanes 2 and 3 after 2 and 4 hours post induction, respectively. These results show that the pHCV-50 fusion protein has an apparent mobility corresponding to a molecular size of 45,000 daltons. This compares acceptably to

the predicted molecular mass of 42,783 daltons.

E. Preparation of HCV CKS-NS5I

Six individual oligonucleotides representing amino acids 2866-3011 of the HCV genome were ligated together and cloned as a 460 base pair EcoRI-BamHI fragment into the CKS fusion vector pJ0200. The resulting plasmid, designated pHCV-49 (SEQ.NO.ID.NO. 12), expresses the HCV CKS-NS5I antigen under control of the lac promoter. The HCV CKS-NS5I antigen consists of 239 amino acids of CKS, eight amino acids contributed by linker DNA sequences, and 146 amino acids from the HCV NS5 region (amino acids 2866-3011). Figure 31 presents a schematic representation of the recombinant antigen expressed by pHCV-49. SEQ.ID.NO. 18 and 19 presents the DNA and amino acid sequence of the HCV CKS-NS5I recombinant antigen produced by pHCV-49. Figure 32 presents the expression of pHCV-49 proteins in E.coli. Lane 1 contained the E.coli lysate containing pHCV-49 expressing HCV CKS-NS5I antigen (amino acids 2866-3011) prior to induction and lanes 2 and 3 after 2 and 4 hours post induction, respectively. These results show that the pHCV-49 fusion protein has an apparent mobility corresponding to a molecular size of 42,000 daltons. This compares acceptably to the predicted molecular mass of 43,497 daltons.

F. Immunoblot of HCV CKS-NS5 Antigens

Induced E.coli lysates containing pHCV-23, pHCV-45, pHCV-48, pHCV-51, pHCV-50, or pHCV-49 were individually run on preparative SDS/PAGE gels to separate the various HCV CKS-NS5 or HCV CKS-BCD recombinant antigens assay from the majority of other E.coli proteins. Gel slices containing the separated individual HCV CKS-NS5 or HCV CKS-BCD recombinant antigens were then electropheretically transferred to nitrocellulose, and the nitrocellulose sheet cut into strips. Figure 40 presents the results of a Western Blot analysis of various serum or plasma samples using these nitrocellulose strips. The arrows on the right indicate the position of each HCV CKS-BCD or HCV CKS-NS5 recombinant antigen, from top to bottom pHCV-23 (HCV CKS-BCD), pHCV-45 (HCV CKS-NS5E), pHCV-48 (HCV CKS-NS5F), pHCV-51 (HCV CKS-NS5G), pHCV-50 (HCV CKS-NS5H), pHCV-49 (HCV CKS-NS5I), and pJO200 (CKS). Panel A contained five normal human plasma, panel B contained five normal human sera, panel C contained twenty human sera positive in the Abbott HCV EIA test, panel D contained two mouse sera directed against CKS, and panel E contained two normal mouse sera. Both the HCV CKS-NS5E antigen expressed by pHCV-45 and the HCV CKS-NS5F antigen expressed by pHCV-48 were immunoreactive when screened with human serum

samples containing HCV antibodies.

EXAMPLE 8. HCV CKS-C100

A. Preparation of HCV CKS-C100 Vectors

Eighteen individual oligonucleotides representing amino acids 1569-1931 of the HCV genome were ligated together and cloned as four separate EcoRI-BamHI subfragments into the CKS fusion vector pJ0200. After subsequent DNA sequences confirmation, the four subfragments were digested with the appropriate restriction enzymes, gel purified, ligated together, and cloned as an 1102 base pair EcoRI-BamHI fragment in the CKS fusion vector pJ0200. The resulting plasmid, designated pHCV-24, expresses the HCV CKS-C100 antigen under control of the lac promoter. The HCV CKS-c100 antigen consists of 239 amino acids of CKS, eight amino acids contributed by linker DNA sequences, 363 amino acids from the HCV NS4 region (amino acids 1569-1931) and 10 additional amino acids contributed by linker DNA sequences. The HCV CKS-c100 antigen was expressed at very low levels by pHCV-24.

Poor expression levels of this HCV CKS-c100 recombinant antigen were overcome by constructing two additional clones containing deletions in the extreme amino terminal portion of the HCV c100 region. The first of these clones, designated pHCV-57 (SEQ.ID.NO. 20 and 21), contains a 23 amino acid deletion (HCV amino acids 1575-1597) and was constructed by deleting a 69 base pair DdeI restriction fragment. The second of these clones, designated pHCV-58 (SEQ.ID.NO. 22 and 23), contains a 21 amino acid deletion (HCV amino acids 1600-1620) and was constructed by deleting a 63 base pair NlaIV-HaeIII restriction fragment. Figure 34 presents a schematic representation of the recombinant antigens expressed by pHCV-24, pHCV-57, and pHCV-58. SEQ.ID. NO. 13 presents the DNA and amino acid sequence of the HCV-C100D1 recombinant antigen produced by pHCV-57. SEQ.ID.NO. 14 presents the DNA and amino acid sequence of the HCV-C100D2 recombinant antigen produced by pHCV-58. Figure 35 presents the expression of pHCV-24, pHCV-57, and pHCV-58 proteins in E.coli. Lane 1 contained the E.coli lysate containing pHCV-24 expressing the HCV CKS-c100 antigen (amino acids 1569-1931) prior to induction and lanes 2 and 3 after 2 and 4 hours post induction, respectively. Lane 4 contained the E.coli lysate containing pHCV-57 expressing the HCV-CKS-C100D1 antigen (amino acids 1569-1574 and 1598-1931) prior to induction and lanes 5 and 6 after 2 and 4 hours induction, respectively. Lane 7 contained the E.coli lysate containing pHCV-58 expressing the HCV CKS-C100D2 antigen (amino acids 1569-1599 and 1621-1931) prior to

induction, and lanes 8 and 9 after 2 and 4 hours induction, respectively. These results show that both the pHCV-57 and pHCV-58 fusion proteins express at significantly higher levels than the pHCV-24 fusion protein and that both the pHCV-57 and pHCV-58 fusion proteins have an apparent mobility corresponding to a molecular size of 65,000 daltons. This compares acceptably to the predicted molecular mass of 64,450 daltons for pHCV-57 and 64,458 daltons for pHCV-58.

EXAMPLE 9. HCV PCR DERIVED EXPRESSION VECTORS

A. Preparation of HCV DNA Fragments

RNA was extracted from the serum of various chimpanzees or humans infected with HCV by first subjecting the samples to digestion with Proteinase K and SDS for 1 hour at 37° centigrade followed by numerous phenol:chloroform extractions. The RNA was then concentrated by several ethanol precipitations and resuspended in water. RNA samples were then reverse transcribed according to supplier's instructions using a specific primer. A second primer was then added and PCR amplification was performed according to supplier's instructions. An aliquot of this PCR reaction was then subjected to an additional round of PCR using nested primers located internal to the first set of primers. In general, these primers also contained restriction endonuclease recognition sequences to be used for subsequent cloning. An aliquot of this second round nested PCR reaction was then subjected to agarose gel electrophoresis and Southern blot analysis to confirm the specificity of the PCR reaction. The remainder of the PCR reaction was then digested with the appropriate restriction enzymes, the HCV DNA fragment of interest gel purified, and ligated to an appropriate cloning vector. This ligation was then transformed into E.coli and single colonies were isolated and plasmid DNA prepared for DNA sequences analysis. The DNA sequences was then evaluated to confirm that the specific HCV coding region of interest was intact. HCV DNA fragments obtained in this manner were then cloned into appropriate vectors for expression analysis.

B. Preparation of HCV CKS-NS3

Using the methods detailed above, a 474 base pair DNA fragment from the putative NS3 region of HCV was generated by PCR. This fragment represents HCV amino acids #1473-1629 and was cloned into the CKS expression vector pJ0201 by blunt-end ligation. The resulting clone, designated pHCV-105, expresses the HCV CKS-NS3 antigen under control of the lac promoter. The HCV CKS-NS3 antigen consists of 239 amino acids of CKS, 12 amino acids contributed by linker DNA sequences, 157 amino acids from the HCV NS3 region (amino acids 1473-1629),

and 9 additional amino acids contributed by linker DNA sequences. Figure 36 presents a schematic representation of the pHCV-105 antigen. SEQ.ID.NO. 24 and 25 presents the DNA and amino acid sequence of the HCV CKS-NS3 recombinant antigen produced by pHCV-105. Figure 37 presents the expression of pHCV-105 proteins in E.coli. Lane 1 contained the E.coli lysate containing pHCV-105 expressing the HCV CKS-NS3 antigen (amino acids 1472-1629) prior to induction and lanes 2 and 3 after 2 and 4 hours induction, respectively. These results show that the pHCV-105 fusion protein has an apparent mobility corresponding to a molecular mass of 43,000 daltons. This compares acceptably to the predicted molecular mass of 46,454 daltons.

C. Preparation of HCV CKS-5'ENV

Using the methods detailed above, a 489 base pair DNA fragment from the putative envelope region of HCV was generated by PCR. This fragment represents the HCV amino acids 114-276 and was cloned into the CKS expression vector pJ0202 using EcoRI-BamHI restriction sites. The resulting clone, designated pHCV-103 (SEQ.ID.NO. 26 and 27), expresses the HCV CKS-5'ENV antigen under control of the lac promoter. The HCV CKS-5'ENV antigen consists of 239 amino acids of CKS, 7 amino acids contributed by linker DNA sequences, 163 amino acids from the HCV envelope region (amino acids 114-276), and 16 additional amino acids contributed by linker DNA sequences. Figure 38 presents a schematic representation of the pHCV-103 antigen. SEQ.ID.NO. 26 and 27 presents the DNA and amino acid sequence of the HCV CKS-5'ENV recombinant antigen produced by pHCV-103. Figure 37 presents the expression of pHCV-103 proteins in E.coli. Lane 1 contained the E.coli lysate containing pHCV-103 expressing the HCV CKS-5'ENV antigen (amino acids 114-276) prior to induction and lanes 5 and 6 after 2 and 4 hours induction, respectively. These results show that the pHCV-103 fusion protein has an apparent mobility corresponding to a molecular mass of 47,000 daltons. This compares acceptably to the predicted molecular mass of 46,091 daltons.

D. Preparation of HCV CKS-3'ENV

Using the methods detailed above, a 621 base pair DNA fragment form the putative envelope region of HCV was generated by PCR. This fragment represents HCV amino acids 263-469 and was cloned into the CKS expression vector pJ0202 using EcoRI restriction sites. The resulting clone, designated pHCV-101 (SEQ.ID.NO. 17), expresses the HCV CKS-3'ENV antigen under control of the lac promoter. The HCV CKS-3'ENV antigen consists of 239 amino acids of CKS, 7 amino acids contributed by linker DNA sequences, 207 amino acids from the HCV

envelope region (amino acids 263-469), and 15 additional amino acids contributed by linker DNA sequences. Figure 39 presents a schematic representation of the pHCV-101 antigen. SEQ.ID.NO. 28 and 29 presents the DNA and amino acid sequence of the HCV CKS-3'ENV recombinant antigen produced by pHCV-101. Figure 37 presents the expression of pHCV-101 proteins in E.coli Lane 7 contained the E.coli lysate containing pHCV-101 expressing the HCV CKS-3'ENV antigen (amino acids 263-469) prior to induction and lanes 8 and 9 after 2 and 4 hours induction, respectively. These resulting show that the pHCV-101 fusion protein has an apparent mobility corresponding to a molecular mass of 47,000 daltons. This compares acceptably to the predicted molecular mass of 51,181 daltons.

E. Preparation of HCV CKS-NS2

Using the methods detailed above, a 636 base pair DNA fragment from the putative NS2 region of HCV was generated by PCR. This fragment represents the HCV amino acids 994-1205 and was cloned into the CKS expression vector pJ0201 using EcoRI restriction sites. The resulting clone, designated pHCV-102, expresses the HCV CKS-NS2 antigen under control of the lac promoter. The HCV CKS-NS2 antigen consists of 239 amino acids of CKS, 7 amino acids contributed by linker DNA sequences, 212 amino acids from the HCV NS2 region (amino acids 994-1205), and 16 additional amino acids contributed by linker DNA sequences. Figure 40 presents a schematic representation of the pHCV-102 antigen. SEQ.ID.NO. 30 and 31 presents the DNA and amino acid sequence of the HCV CKS-NS2 recombinant antigen produced by pHCV-102. Figure 41 presents the expression of pHCV-102 proteins in E.coli. Lane 1 contained the E.coli lysate containing pHCV-102 expressing the HCV CKS-NS2 antigen (amino acids 994-1205) prior to induction and lanes 2 and 3 after 2 and 4 hours induction, respectively. These results show that the pHCV-102 fusion protein has an apparent mobility corresponding to a molecular mass of 53,000 daltons. This compares acceptably to the predicted molecular mass of 51,213 daltons.

F. Preparation of HCV CKS-NS1

Using the methods detailed above, a 654 base pair DNA fragment from the putative NS1 region of HCV was generated by PCR. This fragment represents HCV amino acids 617-834 and was cloned into the CKS expression vector pJ0200 using EcoRI-BamHI restriction sites. The resulting clone, designated pHCV-107, expresses the HCV CKS-NS1 antigen under control of the lac promoter. The HCV CKS-NS1 antigen consists of 239 amino acids of CKS, 10 amino acids contributed by linker DNA sequences, and 218 amino acids from the HCV NS1 region (amino acids 617-834). Figure 42 presents a schematic representation of the pHCV-107

antigen. SEQ.ID.NO. 32 and 33 presents the DNA and amino acid sequence of the HCV CKS-NS1 recombinant antigen produced by pHCV-107.

G. Preparation of HCV CKS-ENV

Using the methods detailed above, a 1068 base pair DNA fragment from the putative envelope region of HCV was generated by PCR. This fragment represents HCV amino acids #114-469 and was cloned into the CKS expression vector pJ0202 using EcoRI restriction sites. The resulting clone, designated pHCV-104, expresses the HCV CKS-ENV antigen under control of the lac promoter. The HCV CKS-ENV antigen consists of 239 amino acids of CKS, 7 amino acids contributed by linker DNA sequences, 356 amino acids from the HCV envelope region (amino acids 114-469), and 15 additional amino acids contributed by linker DNA sequences. Figure 43 presents a schematic representation of the pHCV-104 antigen. SEQ.ID.NO. 34 and 35 presents the DNA and amino acid sequence of the HCV CKS-ENV recombinant antigen produced by pHCV-104.

EXAMPLE 10. HCV CKS-NS1S1

A. Construction of the HCV CKS-NS1S1 Expression Vector

Eight individual oligonucleotides representing amino acids 365-579 of the HCV genome were ligated together and cloned as a 645 base pair EcoRI/BamHI fragment into the CKS fusion vector pJO200. The amino acid sequence of this antigen is designated as pHCV-77 (SEQ. ID. NO. 1). The resultant fusion protein HCV CKS-NS1S1 consists of 239 amino acids of CKS, seven amino acids contributed by linked DNA sequences, and 215 amino acids from the NS1 region of the HCV genome.

B. Production and Characterization of the Recombinant Antigen HCV-NS1S1

pHCV-77 was transformed into E.coli K-12 strain XL-1 (recA1, endA1, gyrA96, thi-1, hsdR17, SupE44, relA1, lac/f1, p10AB, lacI1ADM15, TN10) cells. Expression analysis and characterization of the recombinant protein was done using polyacrylamide gel electrophoresis as described in Example 1. The apparent molecular weight of the pHCV-77 antigen was the same as the expected molecular weight of 50,228 as visualized on a coumassie stained gel. The immunoreactivity as determined by Western blot analysis using human sera indicated that this recombinant antigen was indeed immunoreactive. FIGURE 47A presents the expression of pHCV-77 in E. coli. FIGURE 47B presents an immunoblot of the pHCV-77 antigen expressed in E. coli. Lane 1 contained the E. coli lysate containing pHCV-77 expressing the HCV CKS-NS1S1 antigen prior to induction and Lanes 2 and 3 are 2 and 4 hours post-induction, respectfully.

EXAMPLE 11. HCV CKS-NS1S2

A. Construction of the HCV CKS-NS1S2 Expression Vector

Six individual oligonucleotides representing amino acids 565-731 of the HCV genome was ligated together and cloned as a 501 base pair EcoRI/BamHI fragment into the CKS fusion vector pJO200. The complete amino acid sequence of this antigen is designated as pHCV-65 (SEQ. ID. NO. 2). The resultant fusion protein HCV CKS-NS1S2 consists of 239 amino acids of CKS, eight amino acids contributed by linker DNA sequences, and 167 amino acids from the NS1 region of the HCV genome.

B. Production and Characterization of the Recombinant Antigen HCV-NS1S2

pHCV-65 was transformed into E.coli K-12 strain XL-1 (recA1, endA1, gyrA96, thi-1, hsdR17, SupE44, relA1, lac/f1, p10AB, laclqAMD15, TN10) cells. Expression analysis and characterization of the recombinant protein was done using polyacrylamide gel electrophoresis as described in Example 1. The apparent molecular weight of the pHCV-65 antigen was the same as the expected molecular weight of 46,223 as visualized on a coumassie stained gel. The immunoreactivity as determined by Western blot analyis using human sera indicated that this recombinant antigen was indeed immunoreactive. FIGURE 48A presents the expression of pHCV-65 in E. coli. FIGURE 48B presents an immunoblot of the pHCV-65 antigen expressed in E. coli. Lane 1 contained the E. coli lysate containing pHCV-65 expressing the HCV CKS-NS1S2 antigen prior to induction and Lanes 2 and 3 are 2 and 4 hours post-induction, respectively.

EXAMPLE 12. CKS-NS1S3

A. Construction of the HCV CKS-NS1S3 Expression Vector

Six individual oligonucleotides representing amino acids 717-847 of the HCV genome were ligated together and cloned as a 393 base pair EcoRI/BamHI fragment into the CKS fusion vector pJO200. The complete amino acid sequence of this antigen is designated as pHCV-78 (SEQ. ID. NO. 3). The resultant fusion protein HCV CKS-NS1S3 consists of 239 amino acids of CKS, eight amino acids contributed by linker DNA sequences, and 131 amino acids from the NS1 region of the HCV genome.

B. Production and Characterization of the Recombiant Antigen HCV-NS1S3

pHCV-78 was transformed into E.coli K-12 strain XL-1 (recA1, endA1, gyrA96, thi-1, hsdR17, SupE44, relA1, lac/f1, p10AB, laclqADM15, TN10) cells. Expression analysis and characterization of the recombinant protein was done using

polyacrylamide gel electrophoresis as described in Example 1. Analysis of the coumassie stained gel indicated very low levels of expression of the protein with an expected molecular weight of 42,1141. Western blot analysis also failed to show any immunoreactivity and we are continuing to identify human sera that is specific to this region of NS1.

EXAMPLE 13. CKS-NS1S1-NS1S2

A. Construction of the HCV CKS-NS1S1-NS1S2 Expression Vector

The construction of pHCV-80 (NS1S1-NS1S2) involved using the SACI/BamHI insert from pHCV-65 and ligating that into the SacI/BamHI vector backbone of pHCV-77. The resultant HCV gene represents amino acids 365-731 of the HCV genome. This resulted in a 1101 base pair EcoRI/BamHI fragment of HCV cloned into the CKS fusion vector pJO200. The complete amino acid sequence of this antigen is designated as pHCV-80 (SEQ. ID. NO. 4). The resultant fusion protein HCV CKS NS1S1-NS1S2 consists of 239 amino acids of CKS, seven amino acids contributed by linker DNA sequences, and 367 amino acids from the NS1 region of the HCV genome.

B. Production and Characterization of the Recombinant Antigen HCV-NS1S1-NS1S2

pHCV-80 was transformed into E.coli K-12 strain XL-1 (recA1, endA1, gyrA96, thi-1, hsdR17, SupE44, relA1, lac/f1, p10AB, laclqADM15, TN10) cells. Expression analysis and characterization of the recombinant protein was done using polyacrylamide gel electrophoresis as described in Example 1. The apparent molecular weight of the pHCV-80 antigen was the same as the expected molecular weight of 68,454 as visualized on a coumassie stained gel. The immunoreactivity as determined by Western blot analysis using human sera indicated that this recombinant antigen was very immunoreactive. FIGURE 49A presents the expression of pHCV-80 in E. coli. FIGURE 49B presents an immunoblot of pHCV-80 antigen expressed in E. coli. Lane 1 contained the E. coli lysate containing pHCV-80 expressing the HCV CKS-NS1S1-NS1S2 antigen prior to induction and Lanes 2 and 3 are 2 and 4 hours post-induction, respectively.

EXAMPLE 14. HCV CKS-FULL LENGTH NS1

A. Construction of the HCV CKS-full length NS1 Expression Vector

The construction of pHCV-92 (SEQ. ID. NO. 5) full length NS1) involved using the XhoI/BamHI insert from pHCV-78 (SEQ. ID. NO. 3) and ligating that into the XhoI/BamHI vector backbone of pHCV-80 (SEQ. ID. NO. 4). The resultant HCV gene represents amino acids 365-847 of the HCV genome. This resulted in a 1449

base pair EcoRI/BamHI fragment of HCV cloned into CKS fusion vector pJO200. The complete amino acid sequence of this antigen is designated as pHCV-92 (SEQ. ID. NO. 5). The resultant fusion protein HCV CKS-full length NS1 consists of 239 amino acids of CKS, seven amino acids contributed by linker DNA sequences, and 483 amino acids from the NS1 region of the HCV genome.

B. Production and Characterization of the Recombinant Antigen pHCV-92

pHCV-92 was transformed into E.coli K-12 strain XL-1 (recA1, endA1, gyrA96, thi-1, hsdR17, SupE44, relA1, lac/f1, p10AB, laclqADM15, TN10) cells. Expression analysis and characterization of the recombinant protein was done using polyacrylameide gel electrophoresis as described in Example 1. The expression levels as seen by counassie stained gel were virtually undectable and the Western blot indicated no immunoreactivity. We are still in the process of identifying sera that will recognize this region of HCV NS1.

The present invention thus provides unique recombinant antigens representing distinct antigenic regions of the HCV genome which can be used as reagents for the detection and/or confirmation of antibodies and antigens in test samples from individuals exposed to HCV. The NS1 protein is considered to be a non-structural membrane glycoprotein and to be able to elicit a protective immune response of the host against lethal viral infection.

The recombinant antigens, either alone or in combination, can be used in the assay formats provided herein and exemplified in the Examples. It also is contemplated that these recombinant antigens can be used to develop specific inhibitors of viral replication and used for therapeutic purposes, such as for vaccines. Other applications and modifications of the use of these antigens and the specific embodiments of this inventions as set forth herein, will be apparent to those skilled in the art. Accordingly, the invention is intended to be limited only in accordance with the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: DEVARE, S.
DESAI, S.
DAILEY, S.

(ii) TITLE OF INVENTION: HCV SYNTHETIC PEPTIDE FROM NS1 REGION

(iii) NUMBER OF SEQUENCES: 35

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: ABBOTT LABORATORIES
(B) STREET: ONE ABBOTT PARK ROAD
(C) CITY: ABBOTT PARK
(D) STATE: ILLINOIS
(E) COUNTRY: U.S.
(F) ZIP: 60065-3500

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: POREMBSKI, PRISCILLA E.
(B) REGISTRATION NUMBER: 33,207
(C) REFERENCE/DOCKET NUMBER: 4834PC.02

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 708-937-6365
(B) TELEFAX: 708-937-9556

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 463 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu

1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Thr Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Thr Met Val Gly Asn Trp Ala Lys Val Leu
245 250 255

Val Val Leu Leu Leu Phe Ala Gly Val Asp Ala Glu Thr His Val Thr
260 265 270

Gly Gly Ser Ala Gly His Thr Val Ser Gly Phe Val Ser Leu Leu Ala
275 280 285

Pro Gly Ala Lys Gln Asn Val Gln Leu Ile Asn Thr Asn Gly Ser Trp
290 295 300

His Leu Asn Ser Thr Ala Leu Asn Cys Asn Asp Ser Leu Asn Thr Gly
305 310 315 320

Trp Leu Ala Gly Leu Phe Tyr His His Lys Phe Asn Ser Ser Gly Cys
325 330 335

Pro Glu Arg Leu Ala Ser Cys Arg Pro Leu Thr Asp Phe Asp Gln Gly
340 345 350

Trp Gly Gln Ile Ser Tyr Ala Asn Gly Ser Gly Pro Asp Gln Arg Pro
355 360 365

Tyr Cys Trp His Tyr Pro Pro Lys Pro Cys Gly Ile Val Pro Ala Lys
370 375 380

Ser Val Cys Gly Pro Val Tyr Cys Phe Thr Pro Ser Pro Val Val Val
385 390 395 400

Gly Thr Thr Asp Arg Ser Gly Ala Pro Thr Tyr Ser Trp Gly Glu Asn
405 410 415

Asp Thr Asp Val Phe Val Leu Asn Asn Thr Arg Pro Pro Leu Gly Asn
420 425 430

Trp Phe Gly Cys Thr Trp Met Asn Ser Thr Gly Phe Thr Lys Val Cys
435 440 445

Gly Ala Pro Pro Cys Val Ile Gly Gly Ala Gly Asn Asn Thr Leu
450 455 460

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 414 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Thr Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Met Gly Ala Pro Pro Cys Val Ile Gly Gly
245 250 255

Ala Gly Asn Asn Thr Leu His Cys Pro Thr Asp Cys Phe Arg Lys His
260 265 270

Pro Asp Ala Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro
275 280 285

Arg Cys Leu Val Asp Tyr Pro Tyr Arg Leu Trp His Thr Pro Cys Thr
290 295 300

Ile Asn Thr Thr Ile Phe Lys Ile Arg Met Tyr Val Gly Gly Val Glu
305 310 315 320

His Arg Leu Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp
325 330 335

Leu Glu Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Leu Thr Thr
340 345 350

Thr Gln Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu
355 360 365

Ser Thr Gly Leu Ile His Leu Gly Gln Asn Ile Val Asp Val Gln Tyr
370 375 380

Leu Tyr Gly Val Gly Ser Ser Ile Ala Ser Trp Ala Ile Lys Trp Glu
385 390 395 400

Tyr Val Val Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val
405 410

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 378 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Met Ser Phe Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu Pro
1 5 10 15

Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His Val
20 25 30

Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala Thr
35 40 45

Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu Val
50 55 60

Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala Glu
65 70 75 80

Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn Val
85 90 95

Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val Ala
100 105 110

Asp Asn Leu Ala Gln Arg Gln Val Gly Met Thr Thr Leu Ala Val Pro
115 120 125

Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val Val
130 135 140

Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile Pro
145 150 155 160

Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp Asn
165 170 175

Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile Arg
180 185 190

Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met Leu
195 200 205

Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala Val
210 215 220

Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu Asp
225 230 235 240

Pro Ser Thr Asn Ser Thr Met Glu Tyr Val Val Leu Leu Phe Leu Leu
245 250 255

Leu Ala Asp Ala Arg Val Cys Ser Cys Leu Trp Met Met Leu Leu Ile
260 265 270

Ser Gln Ala Glu Ala Ala Leu Glu Asn Leu Val Ile Leu Asn Ala Ala
275 280 285

Ser Leu Ala Gly Thr His Gly Leu Val Ser Phe Leu Val Phe Phe Cys
290 295 300

Phe Ala Trp Tyr Leu Lys Gly Lys Trp Val Pro Gly Ala Val Tyr Thr
305 310 315 320

Phe Tyr Gly Met Trp Pro Leu Leu Leu Leu Leu Leu Ala Leu Pro Gln
325 330 335

Arg Ala Tyr Ala Leu Asp Thr Glu Val Ala Ala Ser Cys Gly Gly Val
340 345 350

Val Leu Val Gly Leu Met Ala Leu Thr Leu Ser Pro Tyr Tyr Lys Arg
355 360 365

Tyr Ile Ser Trp Cys Leu Trp Trp Leu Gln
370 375

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 622 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Thr Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Thr Met Val Gly Asn Trp Ala Lys Val Leu
245 250 255

Val Val Leu Leu Leu Phe Ala Gly Val Asp Ala Glu Thr His Val Thr
260 265 270

Gly Gly Ser Ala Gly His Thr Val Ser Gly Phe Val Ser Leu Leu Ala
275 280 285

Pro Gly Ala Lys Gln Asn Val Gln Leu Ile Asn Thr Asn Gly Ser Trp

290 295 300

His Leu Asn Ser Thr Ala Leu Asn Cys Asn Asp Ser Leu Asn Thr Gly
305 310 315 320

Trp Leu Ala Gly Leu Phe Tyr His His Lys Phe Asn Ser Ser Gly Cys
325 330 335

Pro Glu Arg Leu Ala Ser Cys Arg Pro Leu Thr Asp Phe Asp Gln Gly
340 345 350

Trp Gly Gln Ile Ser Tyr Ala Asn Gly Ser Gly Pro Asp Gln Arg Pro
355 360 365

Tyr Cys Trp His Tyr Pro Pro Lys Pro Cys Gly Ile Val Pro Ala Lys
370 375 380

Ser Val Cys Gly Pro Val Tyr Cys Phe Thr Pro Ser Pro Val Val Val
385 390 395 400

Gly Thr Thr Asp Arg Ser Gly Ala Pro Thr Tyr Ser Trp Gly Glu Asn
405 410 415

Asp Thr Asp Val Phe Val Leu Asn Asn Thr Arg Pro Pro Leu Gly Asn
420 425 430

Trp Phe Gly Cys Thr Trp Met Asn Ser Thr Gly Phe Thr Lys Val Cys
435 440 445

Gly Ala Pro Pro Cys Val Ile Gly Pro Pro Cys Val Ile Gly Gly Ala
450 455 460

Gly Asn Asn Thr Leu His Cys Pro Thr Asp Cys Phe Arg Lys His Pro
465 470 475 480

Asp Ala Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro Arg
485 490 495

Cys Leu Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr Ile
500 505 510

Asn Tyr Thr Ile Phe Lys Ile Arg Met Tyr Val Gly Gly Val Glu His
515 520 525

Arg Leu Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp Leu
530 535 540

Glu Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Leu Thr Thr Thr
545 550 555 560

Gln Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu Ser
565 570 575

Thr Gly Leu Ile His Leu His Gln Asn Ile Val Asp Val Gln Tyr Leu
580 585 590

Tyr Gly Val Gly Ser Ser Ile Ala Ser Trp Ala Ile Lys Trp Glu Tyr
595 600 605

Val Val Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val Xaa
610 615 620

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 738 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Thr Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Thr Met Val Gly Asn Trp Ala Lys Val Leu
245 250 255

Val Val Leu Leu Leu Phe Ala Gly Val Asp Ala Glu Thr His Val Thr
260 265 270

Gly Gly Ser Ala Gly His Thr Val Ser Gly Phe Val Ser Leu Leu Ala
275 280 285

Pro Gly Ala Lys Gln Asn Val Gln Leu Ile Asn Thr Asn Gly Ser Trp
290 295 300

His Leu Asn Ser Thr Ala Leu Asn Cys Asn Asp Ser Leu Asn Thr Gly
305 310 315 320

Trp Leu Ala Gly Leu Phe Tyr His His Lys Phe Asn Ser Ser Gly Cys
325 330 335

Pro Glu Arg Leu Ala Ser Cys Arg Pro Leu Thr Asp Phe Asp Gln Gly
340 345 350

Trp Gly Gln Ile Ser Tyr Ala Asn Gly Ser Gly Pro Asp Gln Arg Pro
355 360 365

Tyr Cys Trp His Tyr Pro Pro Lys Pro Cys Gly Ile Val Pro Ala Lys
370 375 380

Ser Val Cys Gly Pro Val Tyr Cys Phe Thr Pro Ser Pro Val Val Val
385 390 395 400

Gly Thr Thr Asp Arg Ser Gly Ala Pro Thr Tyr Ser Trp Gly Glu Asn
405 410 415

Asp Thr Asp Val Phe Val Leu Asn Asn Thr Arg Pro Pro Leu Gly Asn
420 425 430

Trp Phe Gly Cys Thr Trp Met Asn Ser Thr Gly Phe Thr Lys Val Cys
435 440 445

Gly Ala Pro Pro Cys Val Ile Gly Pro Pro Cys Val Ile Gly Gly Ala
450 455 460

Gly Asn Asn Thr Leu His Cys Pro Thr Asp Cys Phe Arg Lys His Pro
465 470 475 480

Asp Ala Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro Arg
485 490 495

Cys Leu Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr Ile
500 505 510

Asn Tyr Thr Ile Phe Lys Ile Arg Met Tyr Val Gly Gly Val Glu His
515 520 525

Arg Leu Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp Leu
530 535 540

Glu Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Leu Thr Thr Thr
545 550 555 560

Gln Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu Ser
565 570 575

Thr Gly Leu Ile His Leu His Gln Asn Ile Val Asp Val Gln Tyr Leu
580 585 590

Tyr Gly Val Gly Ser Ser Ile Ala Ser Trp Ala Ile Lys Trp Glu Tyr
595 600 605

Val Val Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val Cys Ser Cys
610 615 620

Leu Trp Met Met Leu Leu Ile Ser Gln Ala Glu Ala Ala Leu Glu Asn
625 630 635 640

Leu Val Ile Leu Asn Ala Ala Ser Leu Ala Gly Thr His Gly Leu Val
645 650 655

Ser Phe Leu Val Phe Phe Cys Phe Ala Trp Tyr Leu Lys Gly Lys Trp
660 665 670

Val Pro Gly Ala Val Tyr Thr Phe Tyr Gly Met Trp Pro Leu Leu Leu
675 680 685

Leu Leu Leu Ala Leu Pro Gln Arg Ala Tyr Ala Leu Asp Thr Glu Val
690 695 700

Ala Ala Ser Cys Gly Gly Val Val Leu Val Gly Leu Met Ala Leu Thr
705 710 715 720

Leu Ser Pro Tyr Tyr Lys Arg Tyr Ile Ser Trp Cys Leu Trp Trp Leu
725 730 735

Gln Xaa

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4481 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 130..1317

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GAATTAATTC CCATTAATGT GAGTTAGCTC ACTCATTAGG CACCCCAGGC TTTACACTTT 60

ATGTTCCGGC TCGTATTTTG TGTGGAATTG TGAGCGGATA ACAATTGGGC ATCCAGTAAG 120

GAGGTTTAA ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG 168
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser
1 5 10

ACG CGT CTG CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG 216
Thr Arg Leu Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met
15 20 25

ATT GTT CAT GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC 264
Ile Val His Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile
30 35 40 45

ATC GTG GCA ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT 312
Ile Val Ala Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala
50 55 60

GGC GGT GAA GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA 360
Gly Gly Glu Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu
65 70 75

CGT CTG GCG GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG 408
Arg Leu Ala Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val
80 85 90

ATC GTT AAT GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT 456
Ile Val Asn Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile
95 100 105

CGT CAG GTT GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT 504
Arg Gln Val Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr
110 115 120 125

CTG GCG GTG CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG 552
Leu Ala Val Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala
130 135 140

GTG AAA GTG GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC 600
Val Lys Val Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg
145 150 155

GCC ACC ATT CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC 648
Ala Thr Ile Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr
160 165 170

GTT GGC GAT AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA 696
Val Gly Asp Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala
175 180 185

GGC TTT ATC CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC 744
Gly Phe Ile Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His
190 195 200 205

ATC GAA ATG TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC 792
Ile Glu Met Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile
210 215 220

CAT GTT GCT GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT 840
His Val Ala Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro
225 230 235

GAA GAT CTC GAC CCG TCG ACG AAT TCC ATG TCT ACC AAC CCG AAA CCG 888
Glu Asp Leu Asp Pro Ser Thr Asn Ser Met Ser Thr Asn Pro Lys Pro
240 245 250

CAG AAA AAA AAC AAA CGT AAC ACC AAC CGT CGT CCG CAG GAC GTT AAA 936
Gln Lys Lys Asn Lys Arg Asn Thr Asn Arg Arg Pro Gln Asp Val Lys
255 260 265

TTC CCG GGT GGT GGT CAG ATC GTT GGT GGT GTT TAC CTG CTG CCG CGT 984
Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu Pro Arg
270 275 280 285

CGT GGT CCG CGT CTG GGT GTT CGT GCT ACG CGT AAA ACC TCT GAA CGT 1032
Arg Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser Glu Arg
290 295 300

TCT CAG CCG CGT GGG CGT CGT CAG CCG ATC CCG AAA GCT CGT CGT CCG 1080
Ser Gln Pro Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg Arg Pro
305 310 315

GAA GGT CGT ACC TGG GCT CAG CCG GGT TAC CCG TGG CCG CTG TAC GGT 1128
Glu Gly Arg Thr Trp Ala Gln Pro Gly Tyr Pro Trp Pro Leu Tyr Gly
320 325 330

AAC GAA GGT TGC GGT TGG GCT GGT TGG CTG CTG TCT CCG CGT GGA TCT 1176
Asn Glu Gly Cys Gly Trp Ala Gly Trp Leu Leu Ser Pro Arg Gly Ser
335 340 345

CGT CCG TCT TGG GGT CCG ACC GAC CCG CGT CGT CGT TCT CGT AAC CTT 1224
Arg Pro Ser Trp Gly Pro Thr Asp Pro Arg Arg Arg Ser Arg Asn Leu
350 355 360 365

GGT AAA GTT ATC GAT ACC CTG ACC TGC GGT TTC GCT GAC CTG ATG GGT 1272
Gly Lys Val Ile Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu Met Gly

370 375 380

TAC ATA CCG CTG GTT GGA GCT CCG CTG GGT GGT GCT GCT CGT GCT 1317
Tyr Ile Pro Leu Val Gly Ala Pro Leu Gly Gly Ala Ala Arg Ala
385 390 395

TAACCCATGG ATCCTCTAGA CTGCAGGCAT GCTAAGTAAG TAGATCTTGA GCGCGTTCGC 1377

GCTGAAATGC GCTAATTTCA CTTCACGACA CTTCAGCCAA TTTTGGGAGG AGTGTCGTAC 1437

CGTTACGATT TTCCTCAATT TTTCTTTTCA ACAATTGATC TCATTCAGGT GACATCTTTT 1497

ATATTGGCGC TCATTATGAA AGCAGTAGCT TTTATGAGGG TAATCTGAAT GGAACAGCTG 1557

CGTGCCGAAT TAAGCCATTT ACTGGGCGAA AAACTCAGTC GTATTGAGTG CGTCAATGAA 1617

AAAGCGGATA CGGCGTTGTG GGCTTTGTAT GACAGCCAGG GAAACCCAAT GCCGTTAATG 1677

GCAAGAAGCT TAGCCCGCCT AATGAGCGGG CTTTTTTTTC GACGCGAGGC TGGATGGCCT 1737

TCCCCATTAT GATTCTTCTC GCTTCCGGCG GCATCGGGAT GCCCGCGTTG CAGGCCATGC 1797

TGTCCAGGCA GGTAGATGAC GACCATCAGG GACAGCTTCA AGGATCGCTC GCGGCTCTTA 1857

CCAGCCTAAC TTCGATCACT GGACCGCTGA TCGTCACGGC GATTTATGCC GCCTCGGCGA 1917

GCACATGGAA CGGGTTGGCA TGGATTGTAG GCGCCGCCCT ATACCTTGTC TGCCTCCCCG 1977

CGTTGCGTCG CGGTGCATGG AGCCGGGCCA CCTCGACCTG AATGGAAGCC GGCGGCACCT 2037

CGCTAACGGA TTCACCACTC CAAGAATTGG AGCCAATCAA TTCTTGCGGA GAACTGTGAA 2097

TGCGCAAACC AACCCTTGGC AGAACATATC CATCGCGTCC GCCATCTCCA GCAGCCGCAC 2157

GCGGCGCATC TCGGGCAGCG TTGGGTCCTG GCCACGGGTG CGCATGATCG TGCTCCTGTC 2217

GTTGAGGACC CGGCTAGGCT GGCGGGGTTG CCTTACTGGT TAGCAGAATG AATCACCGAT 2277

ACGCGAGCGA ACGTGAAGCG ACTGCTGCTG CAAAACGTCT GCGACCTGAG CAACAACATG 2337

AATGGTCTTC GGTTTCCGTG TTTCGTAAAG TCTGGAAACG CGGAAGTCAG CGCCCTGCAC 2397

CATTATGTTC CGGATCTGCA TCGCAGGATG CTGCTGGCTA CCCTGTGGAA CACCTACATC 2457

TGTATTAACG AAGCGCTTCT TCCGCTTCCT CGCTCACTGA CTCGCTGCGC TCGGTCGTTC 2517

GGCTGCGGCG AGCGGTATCA GCTCACTCAA AGGCGGTAAT ACGGTTATCC ACAGAATCAG 2577

GGGATAACGC AGGAAAGAAC ATGTGAGCAA AAGGCCAGCA AAAGGCCAGG AACCGTAAAA 2637

AGGCCGCGTT GCTGGCGTTT TTCCATAGGC TCCGCCCCCC TGACGAGCAT CACAAAAATC 2697

GACGCTCAAG TCAGAGGTGG CGAAACCCGA CAGGACTATA AAGATACCAG GCGTTTCCCC 2757

CTGGAAGCTC CCTCGTGCGC TCTCCTGTTC CGACCCTGCC GCTTACCGGA TACCTGTCCG 2817

CCTTTCTCCC TTCGGGAAGC GTGGCGCTTT CTCAATGCTC ACGCTGTAGG TATCTCAGTT 2877

CGGTGTAGGT CGTTCGCTCC AAGCTGGGCT GTGTGCACGA ACCCCCCGTT CAGCCCGACC 2937

GCTGCGCCTT ATCCGGTAAC TATCGTCTTG AGTCCAACCC GGTAAGACAC GACTTATCGC 2997

CACTGGCAGC AGCCACTGGT AACAGGATTA GCAGAGCGAG GTATGTAGGC GGTGCTACAG 3057

AGTTCTTGAA GTGGTGGCCT AACTACGGCT ACACTAGAAG GACAGTATTT GGTATCTGCG 3117

CTCTGCTGAA GCCAGTTACC TTCGGAAAAA GAGTTGGTAG CTCTTGATCC GGCAAACAAA 3177

CCACCGCTGG TAGCGGTGGT TTTTTTGTTT GCAAGCAGCA GATTACGCGC AGAAAAAAAG 3237

GATCTCAAGA AGATCCTTTG ATCTTTTCTA CGGGGTCTGA CGCTCAGTGG AACGAAAACT 3297

CACGTTAAGG GATTTTGGTC ATGAGATTAT CAAAAAGGAT CTTCACCTAG ATCCTTTTAA 3357

ATTAAAAATG AAGTTTTAAA TCAATCTAAA GTATATATGA GTAAACTTGG TCTGACAGTT 3417

ACCAATGCTT AATCAGTGAG GCACCTATCT CAGCGATCTG TCTATTTCGT TCATCCATAG 3477

TTGCCTGACT CCCCGTCGTG TAGATAACTA CGATACGGGA GGGCTTACCA TCTGGCCCCA 3537

GTGCTGCAAT GATACCGCGA GACCCACGCT CACCGGCTCC AGATTTATCA GCAATAAACC 3597

AGCCAGCCGG AAGGGCCGAG CGCAGAAGTG GTCCTGCAAC TTTATCCGCC TCCATCCAGT 3657

CTATTAATTG TTGCCGGGAA GCTAGAGTAA GTAGTTCGCC AGTTAATAGT TTGCGCAACG 3717

TTGTTGCCAT TGCTACAGGC ATCGTGGTGT CACGCTCGTC GTTTGGTATG GCTTCATTCA 3777

GCTCCGGTTC CCAACGATCA AGGCGAGTTA CATGATCCCC CATGTTGTGC AAAAAAGCGG 3837

TTAGCTCCTT CGGTCCTCCG ATCGTTGTCA GAAGTAAGTT GGCCGCAGTG TTATCACTCA 3897

TGGTTATGGC AGCACTGCAT AATTCTCTTA CTGTCATGCC ATCCGTAAGA TGCTTTTCTG 3957

TGACTGGTGA GTACTCAACC AAGTCATTCT GAGAATAGTG TATGCGGCGA CCGAGTTGCT 4017

CTTGCCCGGC GTCAACACGG GATAATACCG CGCCACATAG CAGAACTTTA AAAGTGCTCA 4077

TCATTGGAAA ACGTTCTTCG GGGCGAAAAC TCTCAAGGAT CTTACCGCTG TTGAGATCCA 4137

GTTCGATGTA ACCCACTCGT GCACCCAACT GATCTTCAGC ATCTTTTACT TTCACCAGCG 4197

TTTCTGGGTG AGCAAAAACA GGAAGGCAAA ATGCCGCAAA AAAGGGAATA AGGGCGACAC 4257

GGAAATGTTG AATACTCATA CTCTTCCTTT TTCAATATTA TTGAAGCATT TATCAGGGTT 4317

ATTGTCTCAT GAGCGGATAC ATATTTGAAT GTATTTAGAA AAATAAACAA ATAGGGGTTC 4377

CGCGCACATT TCCCCGAAAA GTGCCACCTG ACGTCTAAGA AACCATTATT ATCATGACAT 4437

TAACCTATAA AAATAGGCGT ATCACGAGGC CCTTTCGTCT TCAA 4481

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 396 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Met Ser Thr Asn Pro Lys Pro Gln Lys Lys
245 250 255

Asn Lys Arg Asn Thr Asn Arg Arg Pro Gln Asp Val Lys Phe Pro Gly
260 265 270

Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro
275 280 285

Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro
290 295 300

Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg
305 310 315 320

Thr Trp Ala Gln Pro Gly Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly
325 330 335

Cys Gly Trp Ala Gly Trp Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser
340 345 350

Trp Gly Pro Thr Asp Pro Arg Arg Arg Ser Arg Asn Leu Gly Lys Val
355 360 365

Ile Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro
370 375 380

Leu Val Gly Ala Pro Leu Gly Gly Ala Ala Arg Ala
385 390 395

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5600 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 130..2472

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GAATTAATTC CCATTAATGT GAGTTAGCTC ACTCATTAGG CACCCCAGGC TTTACACTTT 60

ATGTTCCGGC TCGTATTTTG TGTGGAATTG TGAGCGGATA ACAATTGGGC ATCCAGTAAG 120

GAGGTTTAA ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG 168
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser
1 5 10

ACG CGT CTG CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG 216
Thr Arg Leu Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met
15 20 25

ATT GTT CAT GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC 264
Ile Val His Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile
30 35 40 45

ATC GTG GCA ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT 312
Ile Val Ala Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala
50 55 60

GGC GGT GAA GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA 360
Gly Gly Glu Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu
65 70 75

CGT CTG GCG GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG 408
Arg Leu Ala Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val
80 85 90

ATC GTT AAT GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT 456
Ile Val Asn Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile
95 100 105

CGT CAG GTT GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT 504
Arg Gln Val Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr
110 115 120 125

CTG GCG GTG CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG 552
Leu Ala Val Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala
130 135 140

GTG AAA GTG GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC 600
Val Lys Val Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg
145 150 155

GCC ACC ATT CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC 648
Ala Thr Ile Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr
160 165 170

GTT GGC GAT AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA 696
Val Gly Asp Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala
175 180 185

GGC TTT ATC CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC 744
Gly Phe Ile Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His
190 195 200 205

ATC GAA ATG TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC 792
Ile Glu Met Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile
210 215 220

CAT GTT GCT GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT 840
His Val Ala Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro
225 230 235

GAA GAT CTC GAC CCG TCG ACG AAT TCC ATG GCT GTT GAC TTT ATC CCG 888
Glu Asp Leu Asp Pro Ser Thr Asn Ser Met Ala Val Asp Phe Ile Pro
240 245 250

GTT GAA AAT CTC GAG ACT ACT ATG CGT TCT CCG GTT TTC ACT GAC AAC 936
Val Glu Asn Leu Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn
255 260 265

TCT TCT CCG CCG GTT GTT CCG CAG TCT TTC CAG GTT GCT CAC CTG CAT 984
Ser Ser Pro Pro Val Val Pro Gln Ser Phe Gln Val Ala His Leu His
270 275 280 285

GCT CCG ACT GGT TCT GGT AAA TCT ACT AAA GTT CCA GCT GCT TAC GCT 1032
Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala
290 295 300

GCT CAG GGT TAC AAA GTT CTG GTT CTG AAC CCG TCT GTT GCT GCT ACT 1080
Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr
305 310 315

CTG GGT TTC GGC GCC TAC ATG TCT AAA GCT CAC GGT ATC GAC CCG AAC 1128
Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn
320 325 330

ATT CGT ACT GGT GTA CGT ACT ATC ACT ACT GGT TCT CCG ATC ACT TAC 1176
Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ser Pro Ile Thr Tyr
335 340 345

TCT ACT TAC GGT AAA TTC CTG GCT GAC GGT GGT TGC TCT GGT GGT GCT 1224
Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala
350 355 360 365

TAC GAT ATC ATC ATC TGC GAC GAA TGC CAC TCT ACT GAC GCT ACT TCT 1272
Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ala Thr Ser
370 375 380

ATC CTG GGT ATC GGT ACC GTT CTG GAC CAG GCT GAA ACT GCA GGT GCT 1320
Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala
385 390 395

CGT CTG GTT GTT CTG GCT ACT GCT ACT CCG CCG GGT TCT GTT ACT GTT 1368
Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val
400 405 410

CCG CAC CCG AAC ATC GAA GAA GTT GCT CTG TCG ACT ACT GGT GAA ATC 1416
Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu Ile
415 420 425

CCG TTC TAC GGT AAA GCT ATC CCG CTC GAG GTT ATC AAA GGT GGT CGT 1464
Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val Ile Lys Gly Gly Arg

430 435 440 445

CAC CTG ATT TTC TGC CAC TCT AAA AAA AAA TGC GAC GAA CTG GCT GCT 1512
His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala
450 455 460

AAG CTT GTT GCT CTG GGT ATC AAC GCT GTT GCT TAC TAC CGT GGT CTG 1560
Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu
465 470 475

GAC GTT TCT GTT ATC CCG ACT TCT GGT GAC GTT GTT GTT GTG GCC ACT 1608
Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Val Val Val Ala Thr
480 485 490

GAC GCT CTG ATG ACT GGT TAC ACT GGT GAC TTC GAC TCT GTT ATC GAT 1656
Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp
495 500 505

TGC AAC ACT TGC AAT TCG TCG ACC GGT TGC GTT GTT ATC GTT GGT CGT 1704
Cys Asn Thr Cys Asn Ser Ser Thr Gly Cys Val Val Ile Val Gly Arg
510 515 520 525

GTT GTT CTG TCT GGT AAA CCG GCC ATT ATC CCG GAC CGT GAA GTT CTG 1752
Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu
530 535 540

TAC CGT GAG TTC GAC GAA ATG GAA GAA TGC TCT CAG CAC CTG CCG TAC 1800
Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr
545 550 555

ATC GAA CAG GGT ATG ATG CTG GCT GAA CAG TTC AAA CAG AAA GCT CTG 1848
Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu
560 565 570

GGT CTG CTG CAG ACC GCT TCT CGT CAG GCT GAA GTT ATC GCT CCG GCT 1896
Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala
575 580 585

GTT CAG ACC AAC TGG CAG AAA CTC GAG ACC TTC TGG GCT AAA CAC ATG 1944
Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met
590 595 600 605

TGG AAC TTC ATC TCT GGT ATC CAG TAC CTG GCT GGT CTG TCT ACC CTG 1992
Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu
610 615 620

CCG GGT AAC CCG GCT ATC GCA AGC TTG ATG GCT TTC ACC GCT GCT GTT 2040
Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val
625 630 635

ACC TCT CCG CTG ACC ACC TCT CAG ACC CTG CTG TTC AAC ATT CTG GGT 2088
Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly
640 645 650

GGT TGG GTT GCT GCT CAG CTG GCT GCT CCG GGT GCT GCT ACC GCT TTC 2136

Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe
655 660 665

GTT GGT GCT GGT CTG GCT GGT GCT GCT ATC GGT TCT GTA GGC CTG GGT 2184
Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly
670 675 680 685

AAA GTT CTG ATC GAC ATT CTG GCT GGT TAC GGT GCT GGT GTT GCT GGA 2232
Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly
690 695 700

GCT CTG GTT GCT TTC AAA ATC ATG TCT GGT GAA GTT CCG TCT ACC GAA 2280
Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu
705 710 715

GAT CTG GTT AAC CTG CTG CCG GCT ATC CTG TCT CCG GGT GCT CTG GTT 2328
Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val
720 725 730

GTT GGT GTT GTT TGC GCT GCT ATC CTG CGT CGT CAC GTT GGC CCG GGT 2376
Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly
735 740 745

GAA GGT GCT GTT CAG TGG ATG AAC CGT CTG ATC GCT TTC GCT TCT CGT 2424
Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg
750 755 760 765

GGT AAC CAC GTT TCT CCA TGG GAT CCT CTA GAC TGC AGG CAT GCT AAG 2472
Gly Asn His Val Ser Pro Trp Asp Pro Leu Asp Cys Arg His Ala Lys
770 775 780

TAAGTAGATC TTGAGCGCGT TCGCGCTGAA ATGCGCTAAT TTCACTTCAC GACACTTCAG 2532

CCAATTTTGG GAGGAGTGTC GTACCGTTAC GATTTTCCTC AATTTTTCTT TTCAACAATT 2592

GATCTCATTC AGGTGACATC TTTTATATTG GCGCTCATTA TGAAAGCAGT AGCTTTTATG 2652

AGGGTAATCT GAATGGAACA GCTGCGTGCC GAATTAAGCC ATTTACTGGG CGAAAAACTC 2712

AGTCGTATTG AGTGCGTCAA TGAAAAAGCG GATACGGCGT TGTGGGCTTT GTATGACAGC 2772

CAGGGAAACC CAATGCCGTT AATGGCAAGA AGCTTAGCCC GCCTAATGAG CGGGCTTTTT 2832

TTTCGACGCG AGGCTGGATG GCCTTCCCCA TTATGATTCT TCTCGCTTCC GGCGGCATCG 2892

GGATGCCCGC GTTGCAGGCC ATGCTGTCCA GGCAGGTAGA TGACGACCAT CAGGGACAGC 2952

TTCAAGGATC GCTCGCGGCT CTTACCAGCC TAACTTCGAT CACTGGACCG CTGATCGTCA 3012

CGGCGATTTA TGCCGCCTCG GCGAGCACAT GGAACGGGTT GGCATGGATT GTAGGCGCCG 3072

CCCTATACCT TGTCTGCCTC CCCGCGTTGC GTCGCGGTGC ATGGAGCCGG GCCACCTCGA 3132

CCTGAATGGA AGCCGGCGGC ACCTCGCTAA CGGATTCACC ACTCCAAGAA TTGGAGCCAA 3192

TCAATTCTTG CGGAGAACTG TGAATGCGCA AACCAACCCT TGGCAGAACA TATCCATCGC 3252

GTCCGCCATC TCCAGCAGCC GCACGCGGCG CATCTCGGGC AGCGTTGGGT CCTGGCCACG 3312

GGTGCGCATG ATCGTGCTCC TGTCGTTGAG GACCCGGCTA GGCTGGCGGG GTTGCCTTAC 3372

TGGTTAGCAG AATGAATCAC CGATACGCGA GCGAACGTGA AGCGACTGCT GCTGCAAAAC 3432

GTCTGCGACC TGAGCAACAA CATGAATGGT CTTCGGTTTC CGTGTTTCGT AAAGTCTGGA 3492

AACGCGGAAG TCAGCGCCCT GCACCATTAT GTTCCGGATC TGCATCGCAG GATGCTGCTG 3552

GCTACCCTGT GGAACACCTA CATCTGTATT AACGAAGCGC TTCTTCCGCT TCCTCGCTCA 3612

CTGACTCGCT GCGCTCGGTC GTTCGGCTGC GGCGAGCGGT ATCAGCTCAC TCAAAGGCGG 3672

TAATACGGTT ATCCACAGAA TCAGGGGATA ACGCAGGAAA GAACATGTGA GCAAAAGGCC 3732

AGCAAAAGGC CAGGAACCGT AAAAAGGCCG CGTTGCTGGC GTTTTTCCAT AGGCTCCGCC 3792

CCCCTGACGA GCATCACAAA AATCGACGCT CAAGTCAGAG GTGGCGAAAC CCGACAGGAC 3852

TATAAAGATA CCAGGCGTTT CCCCCTGGAA GCTCCCTCGT GCGCTCTCCT GTTCCGACCC 3912

TGCCGCTTAC CGGATACCTG TCCGCCTTTC TCCCTTCGGG AAGCGTGGCG CTTTCTCAAT 3972

GCTCACGCTG TAGGTATCTC AGTTCGGTGT AGGTCGTTCG CTCCAAGCTG GGCTGTGTGC 4032

ACGAACCCCC CGTTCAGCCC GACCGCTGCG CCTTATCCGG TAACTATCGT CTTGAGTCCA 4092

ACCCGGTAAG ACACGACTTA TCGCCACTGG CAGCAGCCAC TGGTAACAGG ATTAGCAGAG 4152

CGAGGTATGT AGGCGGTGCT ACAGAGTTCT TGAAGTGGTG GCCTAACTAC GGCTACACTA 4212

GAAGGACAGT ATTTGGTATC TGCGCTCTGC TGAAGCCAGT TACCTTCGGA AAAAGAGTTG 4272

GTAGCTCTTG ATCCGGCAAA CAAACCACCG CTGGTAGCGG TGGTTTTTTT GTTTGCAAGC 4332

AGCAGATTAC GCGCAGAAAA AAAGGATCTC AAGAAGATCC TTTGATCTTT TCTACGGGGT 4392

CTGACGCTCA GTGGAACGAA AACTCACGTT AAGGGATTTT GGTCATGAGA TTATCAAAAA 4452

GGATCTTCAC CTAGATCCTT TTAAATTAAA AATGAAGTTT TAAATCAATC TAAAGTATAT 4512

ATGAGTAAAC TTGGTCTGAC AGTTACCAAT GCTTAATCAG TGAGGCACCT ATCTCAGCGA 4572

TCTGTCTATT TCGTTCATCC ATAGTTGCCT GACTCCCCGT CGTGTAGATA ACTACGATAC 4632

GGGAGGGCTT ACCATCTGGC CCCAGTGCTG CAATGATACC GCGAGACCCA CGCTCACCGG 4692

CTCCAGATTT ATCAGCAATA AACCAGCCAG CCGGAAGGGC CGAGCGCAGA AGTGGTCCTG 4752

CAACTTTATC CGCCTCCATC CAGTCTATTA ATTGTTGCCG GGAAGCTAGA GTAAGTAGTT 4812

CGCCAGTTAA TAGTTTGCGC AACGTTGTTG CCATTGCTAC AGGCATCGTG GTGTCACGCT 4872

CGTCGTTTGG TATGGCTTCA TTCAGCTCCG GTTCCCAACG ATCAAGGCGA GTTACATGAT 4932

CCCCCATGTT GTGCAAAAAA GCGGTTAGCT CCTTCGGTCC TCCGATCGTT GTCAGAAGTA 4992

AGTTGGCCGC AGTGTTATCA CTCATGGTTA TGGCAGCACT GCATAATTCT CTTACTGTCA 5052

TGCCATCCGT AAGATGCTTT TCTGTGACTG GTGAGTACTC AACCAAGTCA TTCTGAGAAT 5112

AGTGTATGCG GCGACCGAGT TGCTCTTGCC CGGCGTCAAC ACGGGATAAT ACCGCGCCAC 5172

ATAGCAGAAC TTTAAAAGTG CTCATCATTG GAAAACGTTC TTCGGGGCGA AAACTCTCAA 5232

GGATCTTACC GCTGTTGAGA TCCAGTTCGA TGTAACCCAC TCGTGCACCC AACTGATCTT 5292

CAGCATCTTT TACTTTCACC AGCGTTTCTG GGTGAGCAAA AACAGGAAGG CAAAATGCCG 5352

CAAAAAAGGG AATAAGGGCG ACACGGAAAT GTTGAATACT CATACTCTTC CTTTTTCAAT 5412

ATTATTGAAG CATTTATCAG GGTTATTGTC TCATGAGCGG ATACATATTT GAATGTATTT 5472

AGAAAAATAA ACAAATAGGG GTTCCGCGCA CATTTCCCCG AAAAGTGCCA CCTGACGTCT 5532

AAGAAACCAT TATTATCATG ACATTAACCT ATAAAAATAG GCGTATCACG AGGCCCTTTC 5592

GTCTTCAA 5600

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 781 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn

85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Met Ala Val Asp Phe Ile Pro Val Glu Asn
245 250 255

Leu Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro
260 265 270

Pro Val Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr
275 280 285

Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly
290 295 300

Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe
305 310 315 320

Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr
325 330 335

Gly Val Arg Thr Ile Thr Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr
340 345 350

Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile
355 360 365

Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ala Thr Ser Ile Leu Gly
370 375 380

Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val
385 390 395 400

Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro
405 410 415

Asn Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr
420 425 430

Gly Lys Ala Ile Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu Ile
435 440 445

Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Val
450 455 460

Ala Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser
465 470 475 480

Val Ile Pro Thr Ser Gly Asp Val Val Val Val Ala Thr Asp Ala Leu
485 490 495

Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr
500 505 510

Cys Asn Ser Ser Thr Gly Cys Val Val Ile Val Gly Arg Val Val Leu
515 520 525

Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu
530 535 540

Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln
545 550 555 560

Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu
565 570 575

Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val Gln Thr
580 585 590

Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met Trp Asn Phe
595 600 605

Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn
610 615 620

Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro
625 630 635 640

Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val
645 650 655

Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala
660 665 670

Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu
675 680 685

Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val
690 695 700

Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val
705 710 715 720

Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val
725 730 735

Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala
740 745 750

Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His
755 760 765

Val Ser Pro Trp Asp Pro Leu Asp Cys Arg His Ala Lys
770 775 780

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1548 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1548

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACG AAT TCC CCA TGG ACC CAC TAC GTT CCG GAA TCT GAC 768
Asp Pro Ser Thr Asn Ser Pro Trp Thr His Tyr Val Pro Glu Ser Asp
245 250 255

GCT GCT GCT CGA GTT ACC GCT ATC CTG TCT TCT CTG ACC GTT ACC CAG 816
Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln
260 265 270

CTT CTG CGT CGT CTG CAC CAG TGG ATC TCT TCT GAA TGC ACC ACC CCG 864
Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro
275 280 285

TGC TCT GGT TCT TGG CTG CGT GAC ATC TGG GAC TGG ATC TGC GAA GTT 912
Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val
290 295 300

CTG TCT GAC TTC AAA ACC TGG CTG AAA GCT AAA CTG ATG CCG CAG CTG 960
Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu
305 310 315 320

CCG GGT ATC CCG TTC GTT TCT TGC CAG CGT GGT TAC AAA GGT GTT TGG 1008
Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp
325 330 335

CGT GTT GAC GGT ATC ATG CAC ACC CGT TGC CAC TGC GGT GCT GAA ATC 1056
Arg Val Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile
340 345 350

ACC GGT CAC GTT AAA AAC GGT ACC ATG CGT ATC GTT GGT CCG CGT ACC 1104
Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr
355 360 365

TGC CGT AAC ATG TGG TCT GGC ACC TTC CCG ATC AAC GCT TAC ACC ACC 1152
Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr
370 375 380

GGT CCG TGC ACC CCG CTG CCG GCT CCG AAC TAC ACC TTC GCT CTG TGG 1200
Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp
385 390 395 400

CGT GTT TCT GCT GAA GAA TAC GTT GAA ATC CGT CAG GTT GGT GAC TTC 1248
Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe
405 410 415

CAC TAC GTT ACC GGT ATG ACC ACC GAC AAC CTG AAA TGC CCG TGC CAG 1296
His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln
420 425 430

GTT CCG TCT CCG GAG TTC TTC ACC GAA CTG GAC GGT GTT CGT CTG CAC 1344
Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His
435 440 445

CGT TTC GCT CCG CCG TGC AAA CCG CTG CTG CGT GAA GAA GTT TCT TTC 1392
Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe
450 455 460

CGT GTT GGT CTG CAC GAA TAC CCG GTT GGT TCT CAG CTG CCG TGC GAA 1440
Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu
465 470 475 480

CCG GAA CCG GAC GTT GCT GTT CTG ACC TCT ATG CTG ACC GAC CCG TCT 1488
Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser
485 490 495

CAC ATC ACC GCT GAA GCT GCT GGT CGT CGA CTG GAT CCT CTA GAC TGC 1536
His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Asp Pro Leu Asp Cys
500 505 510

AGG CAT GCT AAG 1548
Arg His Ala Lys
515

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 516 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Pro Trp Thr His Tyr Val Pro Glu Ser Asp
245 250 255

Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln
260 265 270

Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro
275 280 285

Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val
290 295 300

Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu
305 310 315 320

Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp
325 330 335

Arg Val Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile
340 345 350

Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr
355 360 365

Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr
370 375 380

Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp
385 390 395 400

Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe
405 410 415

His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln
420 425 430

Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His
435 440 445

Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe
450 455 460

Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu
465 470 475 480

Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser
485 490 495

His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Asp Pro Leu Asp Cys
500 505 510

Arg His Ala Lys
515

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1623 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1623

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACG AAT TCT ATG CGT CGA CTG GCT CGT GGT TCT CCG CCG 768
Asp Pro Ser Thr Asn Ser Met Arg Arg Leu Ala Arg Gly Ser Pro Pro
245 250 255

TCT GTT GCT TCT TCT TCT GCT TCT CAA CTG TCT GCT CCG TCT CTG AAA 816
Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys
260 265 270

GCT ACC TGC ACC GCT AAC CAC GAC TCT CCG GAC GCT GAA CTG ATC GAA 864
Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile Glu
275 280 285

GCT AAC CTG CTG TGG CGT CAG GAA ATG GGT GGT AAC ATC ACC CGT GTT 912
Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val
290 295 300

GAA TCT GAA AAC AAA GTT GTT ATC CTG GAC TCT TTC GAC CCG CTG GTT 960
Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu Val
305 310 315 320

GCT GAA GAA GAC GAA CGT GAG ATC TCT GTT CCG GCT GAA ATC CTG CGT 1008
Ala Glu Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu Arg
325 330 335

AAA TCT CGT CGT TTC GCT CAG GCT CTG CCG GTT TGG GCT CGT CCG GAC 1056
Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro Asp
340 345 350

TAC AAC CCG CCG CTG GTT GAA ACC TGG AAA AAA CCG GAC TAC GAA CCG 1104
Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu Pro
355 360 365

CCG GTT GTT CAC GGT TGC CCG CTG CCG CCG CCG AAA TCT CCG CCG GTT 1152
Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro Val
370 375 380

CCG CCG CCG CGT AAA AAA CGT ACC GTT GTT CTG ACC GAA TCT ACC CTG 1200
Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr Leu
385 390 395 400

TCT ACC GCT CTG GCT GAA CTG GCT ACC CGT TCT TTC GGT TCT TCT TCT 1248
Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser Ser
405 410 415

ACC TCG GGT ATC ACC GGT GAC AAC ACC ACC ACC TCT TCT GAA CCG GCT 1296
Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala
420 425 430

CCG TCT GGT TGC CCG CCG GAC TCT GAC GCT GAA TCT TAC TCT TCT ATG 1344
Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met
435 440 445

CCG CCG CTG GAA GGT GAA CCG GGT GAC CCG GAT CTG TCT GAC GGT TCT 1392
Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser
450 455 460

TGG TCT ACC GTT TCT TCT GAA GCT AAC GCT GAA GAC GTT GTT TGC TGC 1440
Trp Ser Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys
465 470 475 480

TCT ATG TCT TAC TCT TGG ACC GGT GCT CTG GTT ACT CCG TGC GCT GCT 1488
Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala
485 490 495

GAA GAA CAG AAA CTG CCG ATC AAC GCT CTG TCT AAC TCT CTG CTG CGT 1536
Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg
500 505 510

CAC CAC AAC CTG GTT TAC TCT ACC ACC TCT CGT TCT GCT TGC CAG CGT 1584
His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg
515 520 525

CAG AAA AAA GTT ACC TTC GAC CGT CTG CAA GTT CTA GAC 1623
Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp
530 535 540

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 541 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Met Arg Arg Leu Ala Arg Gly Ser Pro Pro
245 250 255

Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys

260 265 270

Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile Glu
275 280 285

Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val
290 295 300

Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu Val
305 310 315 320

Ala Glu Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu Arg
325 330 335

Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro Asp
340 345 350

Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu Pro
355 360 365

Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro Val
370 375 380

Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr Leu
385 390 395 400

Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser Ser
405 410 415

Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala
420 425 430

Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met
435 440 445

Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser
450 455 460

Trp Ser Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys
465 470 475 480

Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala
485 490 495

Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg
500 505 510

His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg
515 520 525

Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp
530 535 540

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1488 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1488

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG     48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
 1               5                  10                  15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT     96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
            20              25              30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA    144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
        35              40              45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA    192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
    50              55              60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG    240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65              70              75              80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT    288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
                85              90              95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT    336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
            100             105             110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG    384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
        115             120             125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG    432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
    130             135             140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT    480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145             150             155             160
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CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACG AAT TCT CTA GAC TCC CAC TAC CAG GAC GTT CTG AAA 768
Asp Pro Ser Thr Asn Ser Leu Asp Ser His Tyr Gln Asp Val Leu Lys
245 250 255

GAA GTT AAA GCT GCT GCT TCT AAA GTT AAA GCT AAC CTG CTG TCT GTT 816
Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser Val
260 265 270

GAA GAA GCA TGC TCT CTG ACC CCG CCG CAC TCT GCT AAA TCT AAA TTC 864
Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys Phe
275 280 285

GGT TAC GGT GCT AAA GAC GTT CGT TGC CAC GCT CGT AAA GCT GTT ACC 912
Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val Thr
290 295 300

CAC ATC AAC TCT GTT TGG AAA GAT CTG CTG GAA GAC AAC GTT ACC CCG 960
His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr Pro
305 310 315 320

ATC GAC ACC ACC ATC ATG GCT AAA AAC GAA GTT TTC TGC GTT CAG CCG 1008
Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro
325 330 335

GAA AAA GGT GGT CGT AAA CCG GCT CGT CTG ATC GTT TTC CCG GAC CTG 1056
Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu
340 345 350

GGT GTT CGT GTT TGC GAA AAA ATG GCT CTG TAC GAC GTT GTT ACC AAA 1104
Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr Lys
355 360 365

CTG CCG CTG GCT GTT ATG GGT TCT TCT TAC GGT TTC CAG TAC TCT CCG 1152
Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro
370 375 380

GGT CAG CGT GTT GAG TTC CTG GTT CAG GCT TGG AAA TCT AAA AAA ACC 1200
Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys Thr
385 390 395 400

CCG ATG GGT TTC TCT TAC GAC ACC CGT TGC TTC GAC TCT ACC GTT ACC 1248
Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr
405 410 415

GAA TCT GAC ATT CGT ACC GAA GAA GCT ATC TAC CAG TGC TGC GAC CTG 1296
Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp Leu
420 425 430

GAC CCG CAG GCT CGT GTT GCT ATC AAA TCT CTG ACC GAA CGT CTG TAC 1344
Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu Tyr
435 440 445

GTT GGT GGT CCG CTG ACC AAC TCT CGG GGT GAA AAC TGC GGT TAC CGT 1392
Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr Arg
450 455 460

CGT TGC CGT GCT TCT GGT GTT CTG ACC ACC TCT TGC GGT AAC ACC CTG 1440
Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu
465 470 475 480

ACC TGC TAC ATC AAA GCT CGT GCT GCT TGC CGT GCT GCT GGT CTG CAG 1488
Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu Gln
485 490 495

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 496 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Leu Asp Ser His Tyr Gln Asp Val Leu Lys
245 250 255

Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser Val
260 265 270

Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys Phe
275 280 285

Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val Thr
290 295 300

His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr Pro
305 310 315 320

Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro
325 330 335

Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu
340 345 350

Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr Lys
355 360 365

Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro
370 375 380

Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys Thr
385 390 395 400

Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr
405 410 415

Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp Leu
420 425 430

Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu Tyr
435 440 445

Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr Arg
450 455 460

Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu
465 470 475 480

Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu Gln
485 490 495

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1161 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1161

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu

50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACG AAT TGC ATG CTG CAG GAC TGC ACC ATG CTG GTT TGC 768
Asp Pro Ser Thr Asn Cys Met Leu Gln Asp Cys Thr Met Leu Val Cys
245 250 255

GGT GAC GAC CTG GTT GTT ATC TGC GAA TCT GCT GGT GTT CAG GAA GAC 816
Gly Asp Asp Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp
260 265 270

GCT GCT TCT CTG CGT GCT TTC ACC GAA GCT ATG ACC CGT TAC TCT GCT 864

Ala Ala Ser Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala
275 280 285

CCC CCG GGT GAC CCG CCG CAG CCG GAA TAC GAC CTG GAA CTG ATC ACC 912
Pro Pro Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr
290 295 300

TCT TGC TCT TCT AAC GTT TCT GTT GCT CAC GAC GGT GCT GGT AAA CGT 960
Ser Cys Ser Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg
305 310 315 320

GTT TAC TAC CTG ACC CGT GAC CCG ACC ACC CCG CTG GCT CGT GCT GCT 1008
Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala
325 330 335

TGG GAA ACC GCT CGT CAC ACC CCG GTA AAC TCT TGG CTG GGT AAC ATC 1056
Trp Glu Thr Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile
340 345 350

ATC ATG TTC GCT CCG ACC CTG TGG GCC CGT ATG ATC CTG ATG ACC CAC 1104
Ile Met Phe Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His
355 360 365

TTC TTC TCT GTT CTG ATC GCT CGT GAC CAG CTG GAA CAG GCT CTG GAC 1152
Phe Phe Ser Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp
370 375 380

TGC GAG ATC 1161
Cys Glu Ile
385

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 387 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Cys Met Leu Gln Asp Cys Thr Met Leu Val Cys
245 250 255

Gly Asp Asp Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp
260 265 270

Ala Ala Ser Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala
275 280 285

Pro Pro Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr
290 295 300

Ser Cys Ser Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg
305 310 315 320

Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala
325 330 335

Trp Glu Thr Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile
340 345 350

Ile Met Phe Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His

355 360 365

Phe Phe Ser Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp
370 375 380

Cys Glu Ile
385

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1179 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1179

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val

115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACG AAT TCC ATG GAG ATC TAC GGT GCT TGC TAC TCT ATC 768
Asp Pro Ser Thr Asn Ser Met Glu Ile Tyr Gly Ala Cys Tyr Ser Ile
245 250 255

GAA CCG CTG GAC CTG CCG CCG ATC ATT CAG CGT CTG CAC GGT CTG TCT 816
Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly Leu Ser
260 265 270

GCT TTC TCT CTG CAC TCT TAC TCC CCG GGT GAA ATC AAC CGT GTT GCT 864
Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
275 280 285

GCT TGC CTG CGT AAA CTG GGT GTT CCG CCG CTG CGT GCT TGG CGT CAC 912
Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp Arg His
290 295 300

CGT GCT CGT TCT GTT CGT GCT CGT CTG CTG GCT CGT GGT GGC CGT GCT 960
Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg Gly Gly Arg Ala
305 310 315 320

GCT ATC TGC GGT AAA TAC CTG TTC AAC TGG GCT GTT CGT ACC AAA CTG 1008
Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu
325 330 335

AAA CTG ACC CCG ATC GCT GCT GCT GGT CAG CTG GAC CTG TCT GGT TGG 1056

Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp Leu Ser Gly Trp
340 345 350

TTC ACC GCT GGT TAC TCT GGT GGT GAC ATC TAC CAC TCT GTT TCT CAC 1104
Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val Ser His
355 360 365

GCT CGT CCG CGT TGG ATC TGG TTC TGC CTG CTG CTG CTG GCT GCT GGT 1152
Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala Ala Gly
370 375 380

GTT GGT ATC TAC CTG CTG CCG AAC CGT 1179
Val Gly Ile Tyr Leu Leu Pro Asn Arg
385 390

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 393 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile

145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Met Glu Ile Tyr Gly Ala Cys Tyr Ser Ile
245 250 255

Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly Leu Ser
260 265 270

Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
275 280 285

Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp Arg His
290 295 300

Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg Gly Gly Arg Ala
305 310 315 320

Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu
325 330 335

Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp Leu Ser Gly Trp
340 345 350

Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val Ser His
355 360 365

Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala Ala Gly
370 375 380

Val Gly Ile Tyr Leu Leu Pro Asn Arg
385 390

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1791 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1791

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

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ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG    48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
 1               5                  10                  15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT    96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
            20                  25                  30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA   144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
        35                  40                  45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA   192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
    50                  55                  60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG   240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65                  70                  75                  80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT   288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
                85                  90                  95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT   336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
            100                 105                 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG   384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
        115                 120                 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG   432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
    130                 135                 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT   480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145                 150                 155                 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT   528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
                165                 170                 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC   576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
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180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACG AAT TCC ATG GAC GCT CAC TTC CTG TCT CAG GCG CCG 768
Asp Pro Ser Thr Asn Ser Met Asp Ala His Phe Leu Ser Gln Ala Pro
245 250 255

CCG CCG TCT TGG GAT CAG ATG TGG AAA TGC CTG ATC CGT CTG AAA CCG 816
Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro
260 265 270

ACC CTG CAC GGC CCG ACC CCG CTG CTG TAC CGT CTG GGT GCT GTT CAG 864
Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln
275 280 285

AAC GAA ATC ACC CTG ACC CAC CCG GTT ACC AAA TAC ATC ATG ACC TGC 912
Asn Glu Ile Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys
290 295 300

ATG TCT GCT GAT CTA GAA GTT GTT ACC TCT ACC TGG GTT CTG GTT GGT 960
Met Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly
305 310 315 320

GGT GTT CTG GCT GCT CTG GCT GCT TAC TGC CTG TCG ACC GGT TGC GTT 1008
Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val
325 330 335

GTT ATC GTT GGT CGT GTT GTT CTG TCT GGT AAA CCG GCC ATT ATC CCG 1056
Val Ile Val Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro
340 345 350

GAC CGT GAA GTT CTG TAC CGT GAG TTC GAC GAA ATG GAA GAA TGC TCT 1104
Asp Arg Glu Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser
355 360 365

CAG CAC CTG CCG TAC ATC GAA CAG GGT ATG ATG CTG GCT GAA CAG TTC 1152
Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe
370 375 380

AAA CAG AAA GCT CTG GGT CTG CTG CAG ACC GCT TCT CGT CAG GCT GAA 1200
Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu
385 390 395 400

GTT ATC GCT CCG GCT GTT CAG ACC AAC TGG CAG AAA CTC GAG ACC TTC 1248

Val Ile Ala Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe
405 410 415

TGG GCT AAA CAC ATG TGG AAC TTC ATC TCT GGT ATC CAG TAC CTG GCT 1296
Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala
420 425 430

GGT CTG TCT ACC CTG CCG GGT AAC CCG GCT ATC GCA AGC TTG ATG GCT 1344
Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala
435 440 445

TTC ACC GCT GCT GTT ACC TCT CCG CTG ACC ACC TCT CAG ACC CTG CTG 1392
Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu
450 455 460

TTC AAC ATT CTG GGT GGT TGG GTT GCT GCT CAG CTG GCT GCT CCG GGT 1440
Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly
465 470 475 480

GCT GCT ACC GCT TTC GTT GGT GCT GGT CTG GCT GGT GCT GCT ATC GGT 1488
Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly
485 490 495

TCT GTA GGC CTG GGT AAA GTT CTG ATC GAC ATT CTG GCT GGT TAC GGT 1536
Ser Val Gly Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly
500 505 510

GCT GGT GTT GCT GGA GCT CTG GTT GCT TTC AAA ATC ATG TCT GGT GAA 1584
Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu
515 520 525

GTT CCG TCT ACC GAA GAT CTG GTT AAC CTG CTG CCG GCT ATC CTG TCT 1632
Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser
530 535 540

CCG GGT GCT CTG GTT GTT GGT GTT GTT TGC GCT GCT ATC CTG CGT CGT 1680
Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg
545 550 555 560

CAC GTT GGC CCG GGT GAA GGT GCT GTT CAG TGG ATG AAC CGT CTG ATC 1728
His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile
565 570 575

GCT TTC GCT TCT CGT GGT AAC CAC GTT TCT CCA TGG GAT CCT CTA GAC 1776
Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Trp Asp Pro Leu Asp
580 585 590

TGC AGG CAT GCT AAG 1791
Cys Arg His Ala Lys
595

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 597 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Met Asp Ala His Phe Leu Ser Gln Ala Pro
245 250 255

Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro
260 265 270

Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln
275 280 285

Asn Glu Ile Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys
290 295 300

Met Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly
305 310 315 320

Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val
325 330 335

Val Ile Val Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro
340 345 350

Asp Arg Glu Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser
355 360 365

Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe
370 375 380

Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu
385 390 395 400

Val Ile Ala Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe
405 410 415

Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala
420 425 430

Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala
435 440 445

Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu
450 455 460

Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly
465 470 475 480

Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly
485 490 495

Ser Val Gly Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly
500 505 510

Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu
515 520 525

Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser
530 535 540

Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg
545 550 555 560

His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile
565 570 575

Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Trp Asp Pro Leu Asp
580 585 590

Cys Arg His Ala Lys
595

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1797 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1797

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val

100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACG AAT TCC ATG GAC GCT CAC TTC CTG TCT CAG ACC AAA 768
Asp Pro Ser Thr Asn Ser Met Asp Ala His Phe Leu Ser Gln Thr Lys
245 250 255

CAG TCT GGT GAA AAC CTT CCG TAC CTG GTT GCT TAC CAG GCT ACC GTT 816
Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
260 265 270

TGC GCT CGT GCT CAG GCC CCG ACC CCG CTG CTG TAC CGT CTG GGT GCT 864
Cys Ala Arg Ala Gln Ala Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala
275 280 285

GTT CAG AAC GAA ATC ACC CTG ACC CAC CCG GTT ACC AAA TAC ATC ATG 912
Val Gln Asn Glu Ile Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met
290 295 300

ACC TGC ATG TCT GCT GAT CTA GAA GTT GTT ACC TCT ACC TGG GTT CTG 960
Thr Cys Met Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu
305 310 315 320

GTT GGT GGT GTT CTG GCT GCT CTG GCT GCT TAC TGC CTG TCG ACC GGT 1008

Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly
325 330 335

TGC GTT GTT ATC GTT GGT CGT GTT GTT CTG TCT GGT AAA CCG GCC ATT 1056
Cys Val Val Ile Val Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile
340 345 350

ATC CCG GAC CGT GAA GTT CTG TAC CGT GAG TTC GAC GAA ATG GAA GAA 1104
Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu
355 360 365

TGC TCT CAG CAC CTG CCG TAC ATC GAA CAG GGT ATG ATG CTG GCT GAA 1152
Cys Ser Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu
370 375 380

CAG TTC AAA CAG AAA GCT CTG GGT CTG CTG CAG ACC GCT TCT CGT CAG 1200
Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln
385 390 395 400

GCT GAA GTT ATC GCT CCG GCT GTT CAG ACC AAC TGG CAG AAA CTC GAG 1248
Ala Glu Val Ile Ala Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu
405 410 415

ACC TTC TGG GCT AAA CAC ATG TGG AAC TTC ATC TCT GGT ATC CAG TAC 1296
Thr Phe Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr
420 425 430

CTG GCT GGT CTG TCT ACC CTG CCG GGT AAC CCG GCT ATC GCA AGC TTG 1344
Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu
435 440 445

ATG GCT TTC ACC GCT GCT GTT ACC TCT CCG CTG ACC ACC TCT CAG ACC 1392
Met Ala Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr
450 455 460

CTG CTG TTC AAC ATT CTG GGT GGT TGG GTT GCT GCT CAG CTG GCT GCT 1440
Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala
465 470 475 480

CCG GGT GCT GCT ACC GCT TTC GTT GGT GCT GGT CTG GCT GGT GCT GCT 1488
Pro Gly Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala
485 490 495

ATC GGT TCT GTA GGC CTG GGT AAA GTT CTG ATC GAC ATT CTG GCT GGT 1536
Ile Gly Ser Val Gly Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly
500 505 510

TAC GGT GCT GGT GTT GCT GGA GCT CTG GTT GCT TTC AAA ATC ATG TCT 1584
Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser
515 520 525

GGT GAA GTT CCG TCT ACC GAA GAT CTG GTT AAC CTG CTG CCG GCT ATC 1632
Gly Glu Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile
530 535 540

CTG TCT CCG GGT GCT CTG GTT GTT GGT GTT GTT TGC GCT GCT ATC CTG 1680
Leu Ser Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu
545 550 555 560

CGT CGT CAC GTT GGC CCG GGT GAA GGT GCT GTT CAG TGG ATG AAC CGT 1728
Arg Arg His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg
565 570 575

CTG ATC GCT TTC GCT TCT CGT GGT AAC CAC GTT TCT CCA TGG GAT CCT 1776
Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Trp Asp Pro
580 585 590

CTA GAC TGC AGG CAT GCT AAG 1797
Leu Asp Cys Arg His Ala Lys
595

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 599 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Met Asp Ala His Phe Leu Ser Gln Thr Lys
245 250 255

Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
260 265 270

Cys Ala Arg Ala Gln Ala Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala
275 280 285

Val Gln Asn Glu Ile Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met
290 295 300

Thr Cys Met Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu
305 310 315 320

Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly
325 330 335

Cys Val Val Ile Val Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile
340 345 350

Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu
355 360 365

Cys Ser Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu
370 375 380

Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln
385 390 395 400

Ala Glu Val Ile Ala Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu
405 410 415

Thr Phe Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr
420 425 430

Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu

435 440 445

Met Ala Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr
450 455 460

Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala
465 470 475 480

Pro Gly Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala
485 490 495

Ile Gly Ser Val Gly Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly
500 505 510

Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser
515 520 525

Gly Glu Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile
530 535 540

Leu Ser Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu
545 550 555 560

Arg Arg His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg
565 570 575

Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Trp Asp Pro
580 585 590

Leu Asp Cys Arg His Ala Lys
595

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1251 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1251

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His

20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACT CGA ATT CGA GCT CGG TAC CCT GAG ACA ATC ACG CTT 768

Asp Pro Ser Thr Arg Ile Arg Ala Arg Tyr Pro Glu Thr Ile Thr Leu
245 250 255

CCC CAG GAT GCT GTC TCC CGC ACC CAG CGT CGG GGC AGG ACT GGC AGG 816
Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg
260 265 270

GGG AAG CCA GGC ATC TAC AGA TTT GTG GCA CCG GGG GAG CGC CCT TCC 864
Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser
275 280 285

GGC ATG TTC GAC TCG TCC GTC CTC TGC GAG TGC TAT GAC GCG GGC TGG 912
Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Trp
290 295 300

CCT TGG TAT GAG CTC ACA CCC GCC GAG ACC ACA GTT AGG CTA CGA GCG 960
Pro Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala
305 310 315 320

TAC ATG AAC ACC CCG GGA CTC CCC GTG TGC CAA GAC CAT CTT GAA TTT 1008
Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe
325 330 335

TGG GAG GGC GTC TTC ACG GGT CTC ACC CAT ATA GAC GCC CAC TTT CTA 1056
Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu
340 345 350

TCC CAG ACA AAG CAG AGT GGG GAA AAC CTT CCT TAC CTG GTA GCG TAC 1104
Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr
355 360 365

CAA GCC ACC GTG TGC GCT AGA GCT CAA GCC CCT CCC CCA TCG TGG GAC 1152
Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp
370 375 380

CAG ATG TGG AAG TGC TTG ATC CGC CTC AAG CCT ACC CTT CAT GGG CCG 1200
Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro
385 390 395 400

ACC CCC CTG CTA TAC AGA CTG GGC GGG GGA TCC TCT AGA CTG CAG GCA 1248
Thr Pro Leu Leu Tyr Arg Leu Gly Gly Gly Ser Ser Arg Leu Gln Ala
405 410 415

TGC 1251
Cys

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 417 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Arg Ile Arg Ala Arg Tyr Pro Glu Thr Ile Thr Leu
245 250 255

Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg
260 265 270

Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser
275 280 285

Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Trp
290 295 300

Pro Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala
305 310 315 320

Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe
325 330 335

Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu
340 345 350

Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr
355 360 365

Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp
370 375 380

Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro
385 390 395 400

Thr Pro Leu Leu Tyr Arg Leu Gly Gly Gly Ser Ser Arg Leu Gln Ala
405 410 415

Cys

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1275 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1275

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACT CGA ATT CGT AGG TCG CGC AAT TTG GGT AAG GTC ATC 768
Asp Pro Ser Thr Arg Ile Arg Arg Ser Arg Asn Leu Gly Lys Val Ile
245 250 255

GAC ACC CTC ACG TGC GGC TTC GCC GAC CTC ATG GGG TAT ATT CCG CTC 816
Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu
260 265 270

GTC GGC GCC CCT CTT GGA GGC GCT GCC AGG GCC CTG GGC CAT GGC GTC 864
Val Gly Ala Pro Leu Gly Gly Ala Ala Arg Ala Leu Gly His Gly Val
275 280 285

CGG GTT CTG GAA GAC GGC GTG AAC TAT GCG ACA GGG AAT CTT CCT GGT 912
Arg Val Leu Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly
290 295 300

TGC TCT TTC TCT ATC TTC CTT CTG GCC CTG CTC TCT TGC CTG ACC GTG 960
Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val
305 310 315 320

CCC GCA TCA GCC TAC CAA GTA CGC AAC TCC TCG GGC CTT TAC CAT GTC 1008
Pro Ala Ser Ala Tyr Gln Val Arg Asn Ser Ser Gly Leu Tyr His Val
325 330 335

ACC AAT GAT TGC CCC AAC TCG AGT ATT GTG TAC GAG ACG GCC GAT GCC 1056
Thr Asn Asp Cys Pro Asn Ser Ser Ile Val Tyr Glu Thr Ala Asp Ala
340 345 350

ATC CTG CAC ACT CCG GGG TGC GTC CCT TGC GTT CGT GAG GGC AAC GCC 1104
Ile Leu His Thr Pro Gly Cys Val Pro Cys Val Arg Glu Gly Asn Ala
355 360 365

TCG AGA TGT TGG GTG GCG GTG GCC CCC ACA GTG GCC ACC AGG GAT GGA 1152
Ser Arg Cys Trp Val Ala Val Ala Pro Thr Val Ala Thr Arg Asp Gly
370 375 380

AAA CTC CCC GCA ACG CAG CTT CGA CGT CAC ATT GAT CTG CTT GTC GGG 1200
Lys Leu Pro Ala Thr Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly
385 390 395 400

AGC GCC ACC CTC TGT TCG GCC CTC TAC TTA AGG AGC TCG GTA CCC GGG 1248
Ser Ala Thr Leu Cys Ser Ala Leu Tyr Leu Arg Ser Ser Val Pro Gly
405 410 415

GAT CCT CTA GAC TGC AGG CAT GCT AAG 1275
Asp Pro Leu Asp Cys Arg His Ala Lys
420 425

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 425 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Arg Ile Arg Arg Ser Arg Asn Leu Gly Lys Val Ile
245 250 255

Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu
260 265 270

Val Gly Ala Pro Leu Gly Gly Ala Ala Arg Ala Leu Gly His Gly Val
275 280 285

Arg Val Leu Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly
290 295 300

Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val
305 310 315 320

Pro Ala Ser Ala Tyr Gln Val Arg Asn Ser Ser Gly Leu Tyr His Val
325 330 335

Thr Asn Asp Cys Pro Asn Ser Ser Ile Val Tyr Glu Thr Ala Asp Ala
340 345 350

Ile Leu His Thr Pro Gly Cys Val Pro Cys Val Arg Glu Gly Asn Ala
355 360 365

Ser Arg Cys Trp Val Ala Val Ala Pro Thr Val Ala Thr Arg Asp Gly
370 375 380

Lys Leu Pro Ala Thr Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly
385 390 395 400

Ser Ala Thr Leu Cys Ser Ala Leu Tyr Leu Arg Ser Ser Val Pro Gly
405 410 415

Asp Pro Leu Asp Cys Arg His Ala Lys
420 425

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1401 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1401

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACT CGA ATT CTG CTT GTC GGG AGC GCC ACC CTC TGC TCG 768
Asp Pro Ser Thr Arg Ile Leu Leu Val Gly Ser Ala Thr Leu Cys Ser
245 250 255

GCC CTC TAT GTG GGG GAC TTG TGC GGG TCT GTC TTT CTT GTC GGT CAA 816
Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser Val Phe Leu Val Gly Gln

260 265 270

CTG TTC ACT TTC TCC CCC AGG CAG CAC TGG ACA ACG CAA GAC TGC AAC 864
Leu Phe Thr Phe Ser Pro Arg Gln His Trp Thr Thr Gln Asp Cys Asn
275 280 285

TGT TCT ATC TAC CCC GGC CAC GTA ACG GGT CAC CGC ATG GCA TGG GAT 912
Cys Ser Ile Tyr Pro Gly His Val Thr Gly His Arg Met Ala Trp Asp
290 295 300

ATG ATG ATG AAC TGG TCC CCT ACG ACA GCG CTG GTA GTA GCT CAG CTG 960
Met Met Met Asn Trp Ser Pro Thr Thr Ala Leu Val Val Ala Gln Leu
305 310 315 320

CTC AGG GTC CCG CAA GCC ATC TTG GAC ATG ATC GCT GGT GCC CAC TGG 1008
Leu Arg Val Pro Gln Ala Ile Leu Asp Met Ile Ala Gly Ala His Trp
325 330 335

GGA GTC CTA GCG GGC ATA GCG TAT TTC TCC ATG GTG GGG AAC TGG GCG 1056
Gly Val Leu Ala Gly Ile Ala Tyr Phe Ser Met Val Gly Asn Trp Ala
340 345 350

AAG GTC CTG GTA GTG CTG CTG CTA TTT GCC GGC GTT GAC GCG GAA ACC 1104
Lys Val Leu Val Val Leu Leu Leu Phe Ala Gly Val Asp Ala Glu Thr
355 360 365

CAC GTC ACC GGG GGA AGT GCC GGC CAC ATT ACG GCT GGG CTT GTT CGT 1152
His Val Thr Gly Gly Ser Ala Gly His Ile Thr Ala Gly Leu Val Arg
370 375 380

CTC CTT TCA CCA GGC GCC AAG CAG AAC ATC CAA CTG ATC AAC ACC AAC 1200
Leu Leu Ser Pro Gly Ala Lys Gln Asn Ile Gln Leu Ile Asn Thr Asn
385 390 395 400

GGC AGT TGG CAC ATC AAT AGC ACG GCC TTG AAC TGC AAT GAA AGC CTT 1248
Gly Ser Trp His Ile Asn Ser Thr Ala Leu Asn Cys Asn Glu Ser Leu
405 410 415

AAC ACC GGC TGG TTA GCA GGG CTC TTC TAT CAC CAC AAA TTC AAC TCT 1296
Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr His His Lys Phe Asn Ser
420 425 430

TCA GGC TGT CCT GAG AGG GTT GCC AGC TGC CGT CGC CTT ACC GAT TTT 1344
Ser Gly Cys Pro Glu Arg Val Ala Ser Cys Arg Arg Leu Thr Asp Phe
435 440 445

GAC CAG GGC TGG GAA TTC GAG CTC GGT ACC CGG GGA TCC TCT AGA CTG 1392
Asp Gln Gly Trp Glu Phe Glu Leu Gly Thr Arg Gly Ser Ser Arg Leu
450 455 460

CAG GCA TGC 1401
Gln Ala Cys
465

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 467 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Arg Ile Leu Leu Val Gly Ser Ala Thr Leu Cys Ser
245 250 255

Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser Val Phe Leu Val Gly Gln
260 265 270

Leu Phe Thr Phe Ser Pro Arg Gln His Trp Thr Thr Gln Asp Cys Asn
275 280 285

Cys Ser Ile Tyr Pro Gly His Val Thr Gly His Arg Met Ala Trp Asp
290 295 300

Met Met Met Asn Trp Ser Pro Thr Thr Ala Leu Val Val Ala Gln Leu
305 310 315 320

Leu Arg Val Pro Gln Ala Ile Leu Asp Met Ile Ala Gly Ala His Trp
325 330 335

Gly Val Leu Ala Gly Ile Ala Tyr Phe Ser Met Val Gly Asn Trp Ala
340 345 350

Lys Val Leu Val Val Leu Leu Leu Phe Ala Gly Val Asp Ala Glu Thr
355 360 365

His Val Thr Gly Gly Ser Ala Gly His Ile Thr Ala Gly Leu Val Arg
370 375 380

Leu Leu Ser Pro Gly Ala Lys Gln Asn Ile Gln Leu Ile Asn Thr Asn
385 390 395 400

Gly Ser Trp His Ile Asn Ser Thr Ala Leu Asn Cys Asn Glu Ser Leu
405 410 415

Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr His His Lys Phe Asn Ser
420 425 430

Ser Gly Cys Pro Glu Arg Val Ala Ser Cys Arg Arg Leu Thr Asp Phe
435 440 445

Asp Gln Gly Trp Glu Phe Glu Leu Gly Thr Arg Gly Ser Ser Arg Leu
450 455 460

Gln Ala Cys
465

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1422 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1422

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG   48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
 1               5                  10                  15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT   96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
            20                  25                  30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA  144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
        35                  40                  45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA  192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
    50                  55                  60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG  240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65                  70                  75                  80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT  288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
                85                  90                  95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT  336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
            100                 105                 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG  384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
        115                 120                 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG  432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
    130                 135                 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT  480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145                 150                 155                 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT  528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
                165                 170                 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC  576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
            180                 185                 190
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CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACC GAA TTC GGT GAC ATC ATC AAC GGC TTG CCC GTC TCC 768
Asp Pro Ser Thr Glu Phe Gly Asp Ile Ile Asn Gly Leu Pro Val Ser
245 250 255

GCC CGT AGG GGC CAG GAG ATA CTG CTC GGA CCA GCC GAC GGA ATG GTC 816
Ala Arg Arg Gly Gln Glu Ile Leu Leu Gly Pro Ala Asp Gly Met Val
260 265 270

TCC AAG GGG TGG AGG TTG CTG GCG CCC ATC ACG GCG TAC GCC CAG CAG 864
Ser Lys Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ala Gln Gln
275 280 285

ACA AGG GGC CTC CTA GGG TGT ATA ATC ACC AGC CTG ACT GGC CGG GAC 912
Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp
290 295 300

AAA AAC CAA GCG GAG GGT GAG GTC CAG ATT GTG TCA ACT GCT GCC CAA 960
Lys Asn Gln Ala Glu Gly Glu Val Gln Ile Val Ser Thr Ala Ala Gln
305 310 315 320

ACT TTC CTG GCA ACG TGC ATC AAT GGG GTA TGC TGG ACT GTC TAC CAT 1008
Thr Phe Leu Ala Thr Cys Ile Asn Gly Val Cys Trp Thr Val Tyr His
325 330 335

GGG GCC GGA ACG AGG ACC CTC GCA TCA CCC AAG GGT CCT GTT ATC CAG 1056
Gly Ala Gly Thr Arg Thr Leu Ala Ser Pro Lys Gly Pro Val Ile Gln
340 345 350

ATG TAT ACC AAT GTA GAC CAA GAC CTT GTG GGC TGG CCC GCT CCT CAA 1104
Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Pro Ala Pro Gln
355 360 365

GGT GCC CGC TCA TTG ACA CCC TGC ACC TGC GGC TCC TCG GAC CTT TAC 1152
Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr
370 375 380

CTG GTT ACG AGG CAC GCC GAT GTC ATT CCC GTG CGC CGG CGG GGT GAT 1200
Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp
385 390 395 400

AGC AGG GGC AGC CTG CTT TCG CCC CGG CCC ATT TCT TAT TTG AAA GGC 1248
Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Ile Ser Tyr Leu Lys Gly

405 410 415

TCC TCG GGG GGT CCG CTG TTG TGC CCC GCG GGA CAC GCC GTG GGC ATA 1296
Ser Ser Gly Gly Pro Leu Leu Cys Pro Ala Gly His Ala Val Gly Ile
420 425 430

TTC AGG GCC GCG GTG TGT ACC CGT GGA GTG GCT AAG GCG GTG GAC TTT 1344
Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe
435 440 445

GTC CCC GTG GAG AAC CTC GAG ACA ACC ATG AAT TCG AGC TCG GTA CCC 1392
Val Pro Val Glu Asn Leu Glu Thr Thr Met Asn Ser Ser Ser Val Pro
450 455 460

GGG GAT CCT CTA GAC TGC AGG CAT GCT AAG 1422
Gly Asp Pro Leu Asp Cys Arg His Ala Lys
465 470

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 474 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val

130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Glu Phe Gly Asp Ile Ile Asn Gly Leu Pro Val Ser
245 250 255

Ala Arg Arg Gly Gln Glu Ile Leu Leu Gly Pro Ala Asp Gly Met Val
260 265 270

Ser Lys Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ala Gln Gln
275 280 285

Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp
290 295 300

Lys Asn Gln Ala Glu Gly Glu Val Gln Ile Val Ser Thr Ala Ala Gln
305 310 315 320

Thr Phe Leu Ala Thr Cys Ile Asn Gly Val Cys Trp Thr Val Tyr His
325 330 335

Gly Ala Gly Thr Arg Thr Leu Ala Ser Pro Lys Gly Pro Val Ile Gln
340 345 350

Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Pro Ala Pro Gln
355 360 365

Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr
370 375 380

Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp
385 390 395 400

Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Ile Ser Tyr Leu Lys Gly
405 410 415

Ser Ser Gly Gly Pro Leu Leu Cys Pro Ala Gly His Ala Val Gly Ile
420 425 430

Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe
435 440 445

Val Pro Val Glu Asn Leu Glu Thr Thr Met Asn Ser Ser Ser Val Pro
450 455 460

Gly Asp Pro Leu Asp Cys Arg His Ala Lys
465 470

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1401 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1401

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144
Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG ACG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Thr Thr Leu Ala Val
115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACG AAT TCC ACC ATG GGG CAT TAT CCT TGT ACC ATC AAC 768
Asp Pro Ser Thr Asn Ser Thr Met Gly His Tyr Pro Cys Thr Ile Asn
245 250 255

TAC ACC CTG TTC AAA GTC AGG ATG TAC GTG GGA GGG GTC GAG CAC AGG 816
Tyr Thr Leu Phe Lys Val Arg Met Tyr Val Gly Gly Val Glu His Arg
260 265 270

CTG GAA GTT GCT TGC AAC TGG ACG CGG GGC GAA CGT TGT GAT CTG GAC 864
Leu Glu Val Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp Leu Asp
275 280 285

GAC AGG GAC AGG TCC GAG CTC AGC CCG CTG CTG CTG TCC ACC ACT CAG 912
Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Leu Ser Thr Thr Gln
290 295 300

TGG CAG GTC CTT CCG TGT TCC TTC ACG ACC TTG CCA GCC TTG ACC ACC 960
Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu Thr Thr
305 310 315 320

GGC CTC ATC CAC CTC CAC CAG AAC ATC GTG GAC GTG CAA TAC TTG TAC 1008
Gly Leu Ile His Leu His Gln Asn Ile Val Asp Val Gln Tyr Leu Tyr
325 330 335

GGG GTG GGG TCA AGC ATT GTG TCC TGG GCC ATC AAG TGG GAG TAC GTC 1056
Gly Val Gly Ser Ser Ile Val Ser Trp Ala Ile Lys Trp Glu Tyr Val
340 345 350

ATC CTC TTG TTT CTC CTG CTT GCA GAC GCG CGC ATC TGC TCC TGC TTG 1104
Ile Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Ile Cys Ser Cys Leu
355 360 365

TGG ATG ATG TTA CTC ATA TCC CAA GCG GAG GCA GCC TTG GAA AAC CTT 1152
Trp Met Met Leu Leu Ile Ser Gln Ala Glu Ala Ala Leu Glu Asn Leu
370 375 380

GTG TTA CTC AAT GCG GCG TCT CTG GCC GGG ACG CAC GGT CTT GTG TCC 1200
Val Leu Leu Asn Ala Ala Ser Leu Ala Gly Thr His Gly Leu Val Ser
385 390 395 400

TTC CTC GTG TTT TTC TGC TTT GCA TGG TAT CTG AAG GGT AAG TGG GTG 1248
Phe Leu Val Phe Phe Cys Phe Ala Trp Tyr Leu Lys Gly Lys Trp Val
405 410 415

CCC GGA GTG GCC TAC GCC TTC TAC GGG ATG TGG CCT TTC CTC CTG CTC 1296
Pro Gly Val Ala Tyr Ala Phe Tyr Gly Met Trp Pro Phe Leu Leu Leu
420 425 430

CTG TTA GCG TTG CCC CAA CGG GCA TAC GCG CTG GAC ACG GAG ATG GCC 1344
Leu Leu Ala Leu Pro Gln Arg Ala Tyr Ala Leu Asp Thr Glu Met Ala
435 440 445

GCG TCG TGT GGC GGC GTT GTT CTT GTC GGG TTA ATG GCG CTG ACT CTG 1392
Ala Ser Cys Gly Gly Val Val Leu Val Gly Leu Met Ala Leu Thr Leu
450 455 460

TCA CCA TAT 1401
Ser Pro Tyr
465

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 467 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Thr Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Asn Ser Thr Met Gly His Tyr Pro Cys Thr Ile Asn
245 250 255

Tyr Thr Leu Phe Lys Val Arg Met Tyr Val Gly Gly Val Glu His Arg
260 265 270

Leu Glu Val Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp Leu Asp
275 280 285

Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Leu Ser Thr Thr Gln
290 295 300

Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu Thr Thr
305 310 315 320

Gly Leu Ile His Leu His Gln Asn Ile Val Asp Val Gln Tyr Leu Tyr

325 330 335

Gly Val Gly Ser Ser Ile Val Ser Trp Ala Ile Lys Trp Glu Tyr Val
340 345 350

Ile Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Ile Cys Ser Cys Leu
355 360 365

Trp Met Met Leu Leu Ile Ser Gln Ala Glu Ala Ala Leu Glu Asn Leu
370 375 380

Val Leu Leu Asn Ala Ala Ser Leu Ala Gly Thr His Gly Leu Val Ser
385 390 395 400

Phe Leu Val Phe Phe Cys Phe Ala Trp Tyr Leu Lys Gly Lys Trp Val
405 410 415

Pro Gly Val Ala Tyr Ala Phe Tyr Gly Met Trp Pro Phe Leu Leu Leu
420 425 430

Leu Leu Ala Leu Pro Gln Arg Ala Tyr Ala Leu Asp Thr Glu Met Ala
435 440 445

Ala Ser Cys Gly Gly Val Val Leu Val Gly Leu Met Ala Leu Thr Leu
450 455 460

Ser Pro Tyr
465

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1851 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1851

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATG AGT TTT GTG GTC ATT ATT CCC GCG CGC TAC GCG TCG ACG CGT CTG 48
Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

CCC GGT AAA CCA TTG GTT GAT ATT AAC GGC AAA CCC ATG ATT GTT CAT 96
Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

GTT CTT GAA CGC GCG CGT GAA TCA GGT GCC GAG CGC ATC ATC GTG GCA 144

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

ACC GAT CAT GAG GAT GTT GCC CGC GCC GTT GAA GCC GCT GGC GGT GAA 192
Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

GTA TGT ATG ACG CGC GCC GAT CAT CAG TCA GGA ACA GAA CGT CTG GCG 240
Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

GAA GTT GTC GAA AAA TGC GCA TTC AGC GAC GAC ACG GTG ATC GTT AAT 288
Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

GTG CAG GGT GAT GAA CCG ATG ATC CCT GCG ACA ATC ATT CGT CAG GTT 336
Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

GCT GAT AAC CTC GCT CAG CGT CAG GTG GGT ATG GCG ACT CTG GCG GTG 384
Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

CCA ATC CAC AAT GCG GAA GAA GCG TTT AAC CCG AAT GCG GTG AAA GTG 432
Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

GTT CTC GAC GCT GAA GGG TAT GCA CTG TAC TTC TCT CGC GCC ACC ATT 480
Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

CCT TGG GAT CGT GAT CGT TTT GCA GAA GGC CTT GAA ACC GTT GGC GAT 528
Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

AAC TTC CTG CGT CAT CTT GGT ATT TAT GGC TAC CGT GCA GGC TTT ATC 576
Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

CGT CGT TAC GTC AAC TGG CAG CCA AGT CCG TTA GAA CAC ATC GAA ATG 624
Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

TTA GAG CAG CTT CGT GTT CTG TGG TAC GGC GAA AAA ATC CAT GTT GCT 672
Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

GTT GCT CAG GAA GTT CCT GGC ACA GGT GTG GAT ACC CCT GAA GAT CTC 720
Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

GAC CCG TCG ACT CGA ATT CGT AGG TCG CGC AAT TTG GGT AAG GTC ATC 768
Asp Pro Ser Thr Arg Ile Arg Arg Ser Arg Asn Leu Gly Lys Val Ile
245 250 255

GAT ACC CTC ACG TGC GGC TTC GCC GAC CTC ATG GGG TAC ATT CCG CTC 816
Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu
260 265 270

GTC GGC GCC CCT CTT GGA GGC GCT GCC AGG GCC CTG GCG CAT GGC GTC 864
Val Gly Ala Pro Leu Gly Gly Ala Ala Arg Ala Leu Ala His Gly Val
275 280 285

CGG GTT CTG GAA GAC GGC GTG AAC TAT GCA ACA GGG AAC CTT CCC GGT 912
Arg Val Leu Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly
290 295 300

TGC TCT TTC TCT ATC TTC CTT CTG GCC CTG CTC TCT TGC CTG ACT GTG 960
Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val
305 310 315 320

CCC GCG TCA TCC TAC CAA GTA CGC AAC TCC TCG GGC CTT TAT CAT GTC 1008
Pro Ala Ser Ser Tyr Gln Val Arg Asn Ser Ser Gly Leu Tyr His Val
325 330 335

ACC AAT GAT TGC CCC AAC TCG AGC ATT GTG TAC GAG ACG GCC GAT ACC 1056
Thr Asn Asp Cys Pro Asn Ser Ser Ile Val Tyr Glu Thr Ala Asp Thr
340 345 350

ATC CTA CAC TCT CCG GGG TGC GTC CCT TGC GTT CGC GAG GGC AAC ACC 1104
Ile Leu His Ser Pro Gly Cys Val Pro Cys Val Arg Glu Gly Asn Thr
355 360 365

TCG AAA TGT TGG GTG GCG GTG GCC CCC ACA GTG GCC ACC AGG GAC GGC 1152
Ser Lys Cys Trp Val Ala Val Ala Pro Thr Val Ala Thr Arg Asp Gly
370 375 380

AAA CTC CCC TCA ACG CAG CTT CGA CGT CAC ATC GAT CTG CTC GTC GGG 1200
Lys Leu Pro Ser Thr Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly
385 390 395 400

AGC GCC ACC CTC TGC TCG GCC CTC TAT GTG GGG GAC TTG TGC GGG TCT 1248
Ser Ala Thr Leu Cys Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser
405 410 415

GTC TTT CTT GTC AGT CAA CTG TTC ACC TTC TCC CCT AGG CGC CAT TGG 1296
Val Phe Leu Val Ser Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp
420 425 430

ACA ACG CAA GAC TGC AAC TGT TCT ATC TAC CCC GGC CAT ATA ACG GGT 1344
Thr Thr Gln Asp Cys Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly
435 440 445

CAC CGC ATG GCA TGG GAT ATG ATG ATG AAC TGG TCC CCT ACA ACG GCG 1392
His Arg Met Ala Trp Asp Met Met Met Asn Trp Ser Pro Thr Thr Ala
450 455 460

CTG GTA GTA GCT CAG CTG CTC AGG GTC CCA CAA GCC ATC TTG GAC ATG 1440
Leu Val Val Ala Gln Leu Leu Arg Val Pro Gln Ala Ile Leu Asp Met
465 470 475 480

ATC GCA GGT GCC CAC TGG GGA GTC CTA GCG GGC ATA GCG TAT TTC TCC 1488
Ile Ala Gly Ala His Trp Gly Val Leu Ala Gly Ile Ala Tyr Phe Ser
485 490 495

ATG GTG GGG AAC TGG GCG AAG GTC CTG GTA GTG CTG TTG CTG TTT TCC 1536
Met Val Gly Asn Trp Ala Lys Val Leu Val Val Leu Leu Leu Phe Ser
500 505 510

GGC GTC GAT GCG GCA ACC TAC ACC ACC GGG GGG AGC GTT GCT AGG ACC 1584
Gly Val Asp Ala Ala Thr Tyr Thr Thr Gly Gly Ser Val Ala Arg Thr
515 520 525

ACG CAT GGA TTC TCC AGC TTA TTC AGT CAA GGC GCC AAG CAG AAC ATC 1632
Thr His Gly Phe Ser Ser Leu Phe Ser Gln Gly Ala Lys Gln Asn Ile
530 535 540

CAG CTG ATT AAC ACC AAC GGC AGT TGG CAC ATC AAT CGC ACG GCC TTG 1680
Gln Leu Ile Asn Thr Asn Gly Ser Trp His Ile Asn Arg Thr Ala Leu
545 550 555 560

AAC TGT AAT GCG AGC CTC GAC ACT GGC TGG GTA GCG GGG CTC TTC TAT 1728
Asn Cys Asn Ala Ser Leu Asp Thr Gly Trp Val Ala Gly Leu Phe Tyr
565 570 575

TAC CAC AAA TTC AAC TCT TCA GGC TGC CCT GAG AGG ATG GCC AGC TGT 1776
Tyr His Lys Phe Asn Ser Ser Gly Cys Pro Glu Arg Met Ala Ser Cys
580 585 590

AGA CCC CTT GCC GAT TTT GAC CAG GGC TGG GAA TTC GAG CTC GGT ACC 1824
Arg Pro Leu Ala Asp Phe Asp Gln Gly Trp Glu Phe Glu Leu Gly Thr
595 600 605

CGG GGA TCC TCT AGA CTG CAG GCA TGC 1851
Arg Gly Ser Ser Arg Leu Gln Ala Cys
610 615

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 617 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Met Ser Phe Val Val Ile Ile Pro Ala Arg Tyr Ala Ser Thr Arg Leu
1 5 10 15

Pro Gly Lys Pro Leu Val Asp Ile Asn Gly Lys Pro Met Ile Val His
20 25 30

Val Leu Glu Arg Ala Arg Glu Ser Gly Ala Glu Arg Ile Ile Val Ala
35 40 45

Thr Asp His Glu Asp Val Ala Arg Ala Val Glu Ala Ala Gly Gly Glu
50 55 60

Val Cys Met Thr Arg Ala Asp His Gln Ser Gly Thr Glu Arg Leu Ala
65 70 75 80

Glu Val Val Glu Lys Cys Ala Phe Ser Asp Asp Thr Val Ile Val Asn
85 90 95

Val Gln Gly Asp Glu Pro Met Ile Pro Ala Thr Ile Ile Arg Gln Val
100 105 110

Ala Asp Asn Leu Ala Gln Arg Gln Val Gly Met Ala Thr Leu Ala Val
115 120 125

Pro Ile His Asn Ala Glu Glu Ala Phe Asn Pro Asn Ala Val Lys Val
130 135 140

Val Leu Asp Ala Glu Gly Tyr Ala Leu Tyr Phe Ser Arg Ala Thr Ile
145 150 155 160

Pro Trp Asp Arg Asp Arg Phe Ala Glu Gly Leu Glu Thr Val Gly Asp
165 170 175

Asn Phe Leu Arg His Leu Gly Ile Tyr Gly Tyr Arg Ala Gly Phe Ile
180 185 190

Arg Arg Tyr Val Asn Trp Gln Pro Ser Pro Leu Glu His Ile Glu Met
195 200 205

Leu Glu Gln Leu Arg Val Leu Trp Tyr Gly Glu Lys Ile His Val Ala
210 215 220

Val Ala Gln Glu Val Pro Gly Thr Gly Val Asp Thr Pro Glu Asp Leu
225 230 235 240

Asp Pro Ser Thr Arg Ile Arg Arg Ser Arg Asn Leu Gly Lys Val Ile
245 250 255

Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu
260 265 270

Val Gly Ala Pro Leu Gly Gly Ala Ala Arg Ala Leu Ala His Gly Val
275 280 285

Arg Val Leu Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly
290 295 300

Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val
305 310 315 320

Pro Ala Ser Ser Tyr Gln Val Arg Asn Ser Ser Gly Leu Tyr His Val

325 330 335

Thr Asn Asp Cys Pro Asn Ser Ser Ile Val Tyr Glu Thr Ala Asp Thr
340 345 350

Ile Leu His Ser Pro Gly Cys Val Pro Cys Val Arg Glu Gly Asn Thr
355 360 365

Ser Lys Cys Trp Val Ala Val Ala Pro Thr Val Ala Thr Arg Asp Gly
370 375 380

Lys Leu Pro Ser Thr Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly
385 390 395 400

Ser Ala Thr Leu Cys Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser
405 410 415

Val Phe Leu Val Ser Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp
420 425 430

Thr Thr Gln Asp Cys Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly
435 440 445

His Arg Met Ala Trp Asp Met Met Met Asn Trp Ser Pro Thr Thr Ala
450 455 460

Leu Val Val Ala Gln Leu Leu Arg Val Pro Gln Ala Ile Leu Asp Met
465 470 475 480

Ile Ala Gly Ala His Trp Gly Val Leu Ala Gly Ile Ala Tyr Phe Ser
485 490 495

Met Val Gly Asn Trp Ala Lys Val Leu Val Val Leu Leu Leu Phe Ser
500 505 510

Gly Val Asp Ala Ala Thr Tyr Thr Thr Gly Gly Ser Val Ala Arg Thr
515 520 525

Thr His Gly Phe Ser Ser Leu Phe Ser Gln Gly Ala Lys Gln Asn Ile
530 535 540

Gln Leu Ile Asn Thr Asn Gly Ser Trp His Ile Asn Arg Thr Ala Leu
545 550 555 560

Asn Cys Asn Ala Ser Leu Asp Thr Gly Trp Val Ala Gly Leu Phe Tyr
565 570 575

Tyr His Lys Phe Asn Ser Ser Gly Cys Pro Glu Arg Met Ala Ser Cys
580 585 590

Arg Pro Leu Ala Asp Phe Asp Gln Gly Trp Glu Phe Glu Leu Gly Thr
595 600 605

Arg Gly Ser Ser Arg Leu Gln Ala Cys
610 615

CLAIMS

1. A recombinant fusion protein SEQ. ID. NO. 1.
2. A recombinant fusion protein SEQ. ID. NO. 2.
3. A recombinant fusion protein SEQ. ID. NO. 3.
4. A recombinant fusion protein SEQ. ID. NO. 4.
5. A recombinant fusion protein SEQ. ID. NO. 5.
6. A polypeptide SEQ. ID. NO. 1.
7. A polypeptide SEQ. ID. NO. 2.
8. A polypeptide SEQ. ID. NO. 3.
9. A polypeptide SEQ. ID. NO. 4.
10. A polypeptide SEQ. ID. NO. 5.

11. An assay for identifying the presence of an antibody immunologically reactive with an HCV antigen in a fluid sample comprising:

contacting the sample with at least one polypeptide selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5 under conditions suitable for complexing the antibody with the polypeptide; and detecting the antibody-polypeptide complex.

12. In a confirmatory assay for identifying the presence of an antibody in a fluid sample immunologically reactive with an HCV antigen wherein the sample is used to prepare first and second immunologically equivalent aliquots and the first aliquot is contacted with at least one polypeptide selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5 under conditions suitable for complexing the antibody with the polypeptide and wherein the first antibody-antigen complex is detected, and:

contacting the second aliquot with a polypeptide selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5 under conditions suitable to form a second antibody-antigen complex; and detecting the second antibody-antigen complex; wherein the polypeptide selected in the first aliquot is not the same as the polypeptide selected in the second aliquot.

13. In an immunodot assay for identifying the presence of an antibody immunologically reactive with an HCV antigen in a fluid sample wherein the sample is concurrently contacted with at least two polypeptides separately bound to distinct regions of the solid support, each containing distinct epitopes of an HCV antigen under conditions suitable for complexing the antibody with the polypeptide; and detecting the antibody-polypeptide complex, and

wherein said polypeptides are selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5.

14. In a competition assay for identifying the presence of an antibody immunologically reactive with an HCV antigen in a fluid sample wherein the sample is used to prepare first and second immunologically equivalent aliquots wherein the first aliquot is contacted with a polypeptide bound to a solid support under conditions suitable for complexing the antibody with the polypeptide to form a detectable antibody-polypeptide complex, and wherein the second aliquot is first contacted with unbound polypeptide and then contacted with said bound polypeptide wherein the polypeptide is selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5.

15. In a competition assay for identifying the presence of an antibody immunologically reactive with an HCV antigen in a fluid sample wherein the sample is used to prepare first and second immunologically equivalent aliquots wherein the first aliquot is contacted with a polypeptide bound to a solid support under conditions suitable for complexing the antibody with the polypeptide to form a detectable antibody-polypeptide complex and wherein the second aliquot is first contacted with unbound polypeptide and then contacted with said bound polypeptide wherein the polypeptide is selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5; wherein the second aliquot is contacted with unbound and bound polypeptide simultaneously.

16. In a neutralization assay for identifying the presence of an antibody immunologically reactive with an HCV antigen in a fluid sample wherein the sample is used to prepare first and second immunologically equivalent aliquots wherein the

first aliquot is contacted with a polypeptide bound to a solid support under conditions suitable for complexing the antibody with the polypeptide to form a detectable antibody-polypeptide complex wherein the bound polypeptide is selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5;

and wherein the second aliquot is first contacted with unbound polypeptide and then contacted with said bound polypeptide wherein the unbound polypeptide is selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5 and wherein the bound polypeptide selected is not the same as the same as the unbound polypeptide selected.

17. In a neutralization assay for identifying the presence of an antibody immunologically reactive with an HCV antigen in a fluid sample wherein the sample is used to prepare first and second immunologically equivalent aliquots wherein the first aliquot is contacted with a polypeptide bound to a solid support under conditions suitable for complexing the antibody with the polypeptide to form a detectable antibody-polypeptide complex wherein the bound polypeptide is selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5;

and wherein the second aliquot is first contacted with unbound polypeptide and then contacted with said bound polypeptide wherein the unbound polypeptide is selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5;

and wherein the bound polypeptide selected is not the same as the unbound polypeptide selected;

and wherein the second aliquot is contacted with unbound and bound polypeptide simultaneously.

18. An immunoassay kit comprising:

a polypeptide containing at least one HCV antigen selected from the group consisting of recombinant fusion proteins SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and polypeptides SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5;

one or more sample preparation reagents;

and one or more detection and signal producing reagents.

19. A kit of claim 18 wherein the polypeptides are bound to a solid support.

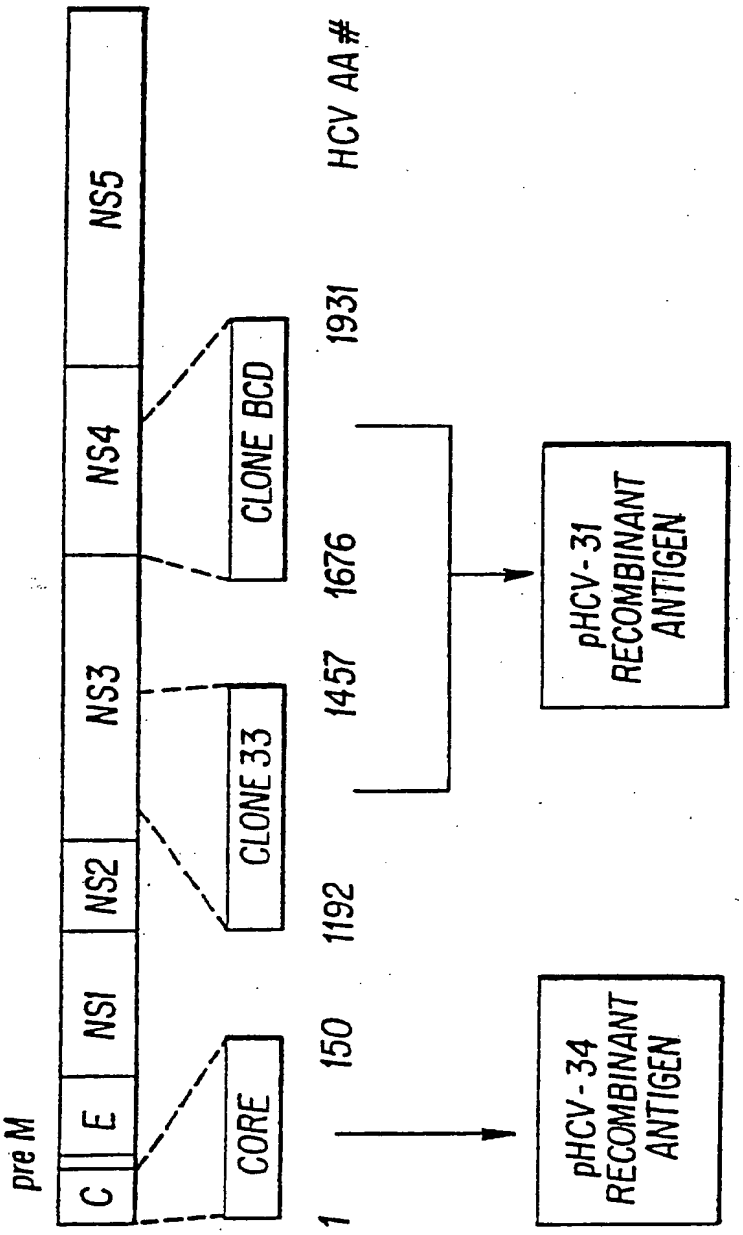


FIG. 1

SEROLOGIC PROFILE OF CHIMPANZEES INOCULATED WITH HEPATITIS C VIRUS									
			ALT (mIU/ml) ELEVATION* (DPI)				DETECTION OF SEROCONVERSION TO HCV PROTEINS		
ID #	NAME	Pre ** (range)	First	Peak	Duration	Maximum value	C100 – 3 (DPI)	pHCV-31 pHCV-34 (DPI)	DAYS DIFFERENT
CH 427	COLONEL	29 - 53	56	75	24	280	77	56	21
CH 479	JR	14 - 20	91	91	7	156	133	98	35
CH 477	KIST	17 - 31	30	35	12	107	70	70	0
CH 335	LEO	16 - 20	38	46	21	295	59	38	21
CH 120	LOLITA	15 - 28	33	65	39	435	65	100	35
CH 21	MELILOT	12 - 30	68	75	14	190	82	66	16
CH 379	PAN	19 - 27	49	68	28	250	119	98	21

* twice the upper limit of normal values
** eleven preinoculation samples per animal

FIG. 2

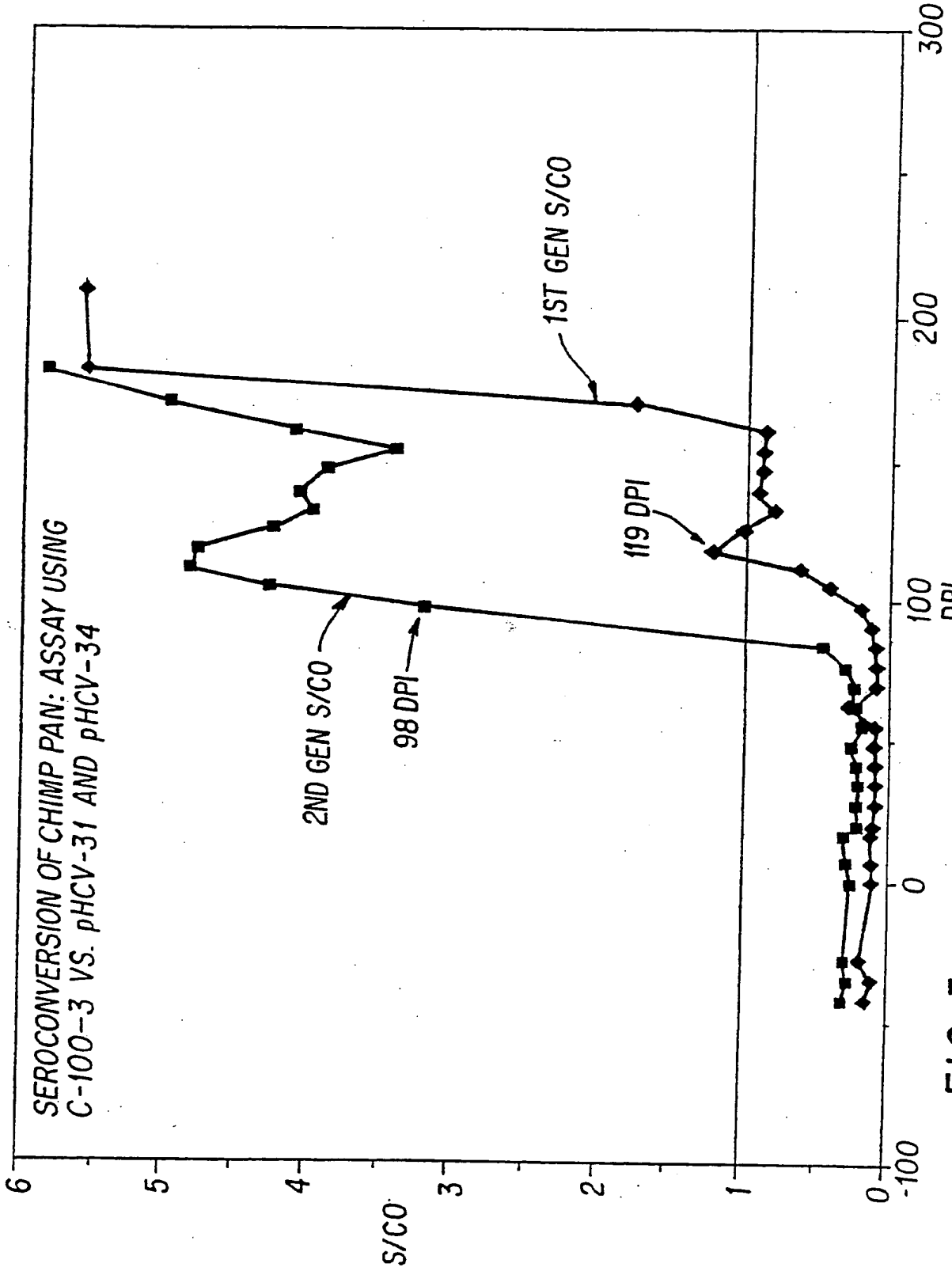


FIG. 3

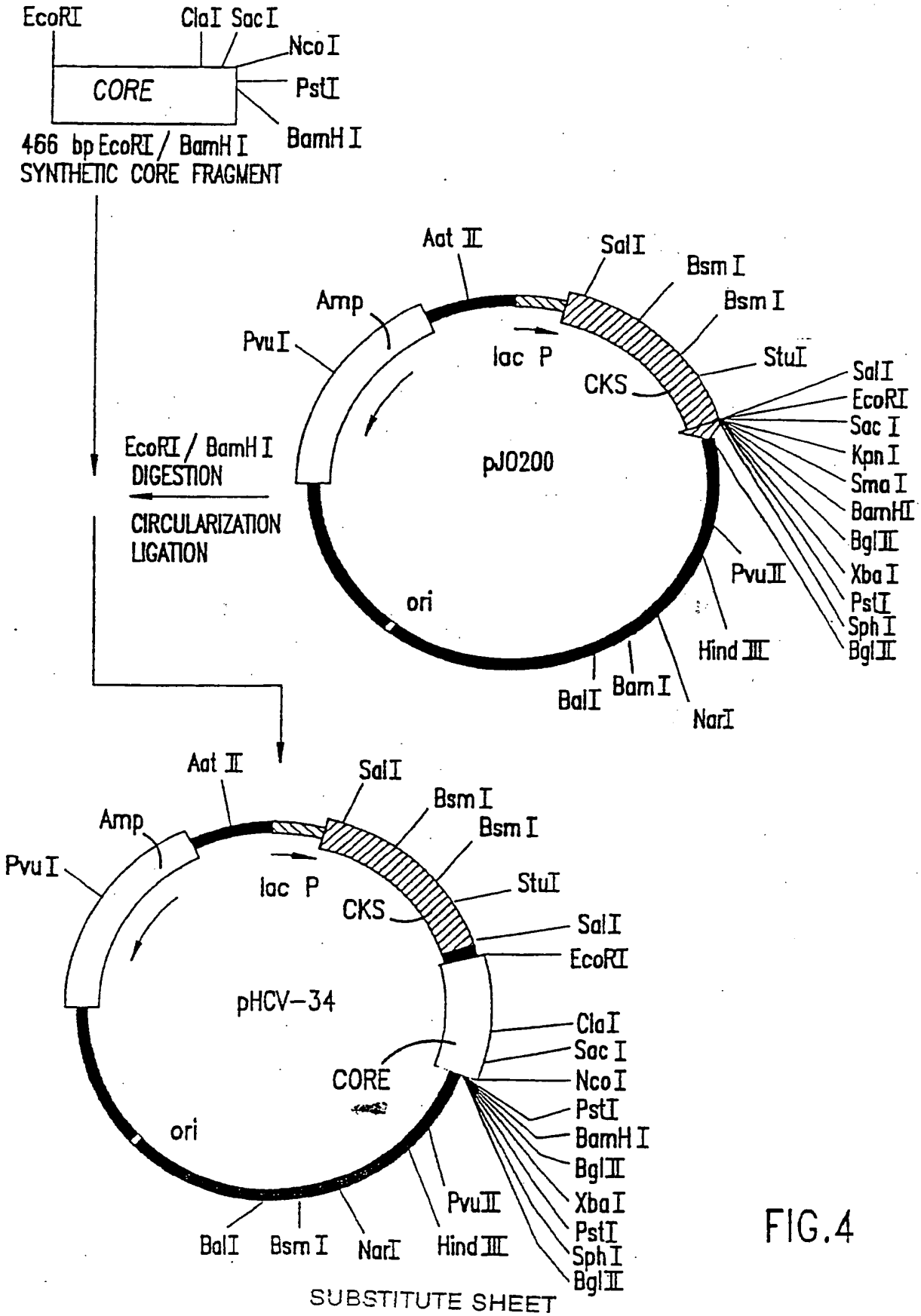


FIG.4

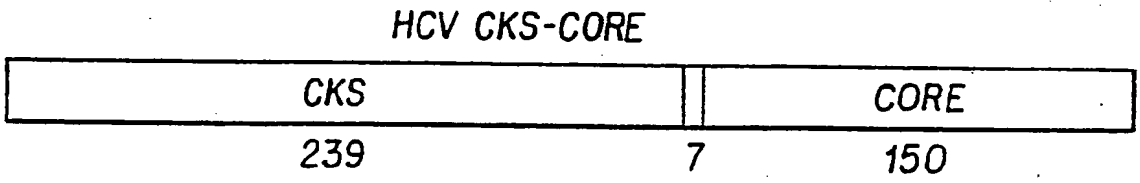


FIG. 5

1 2 3

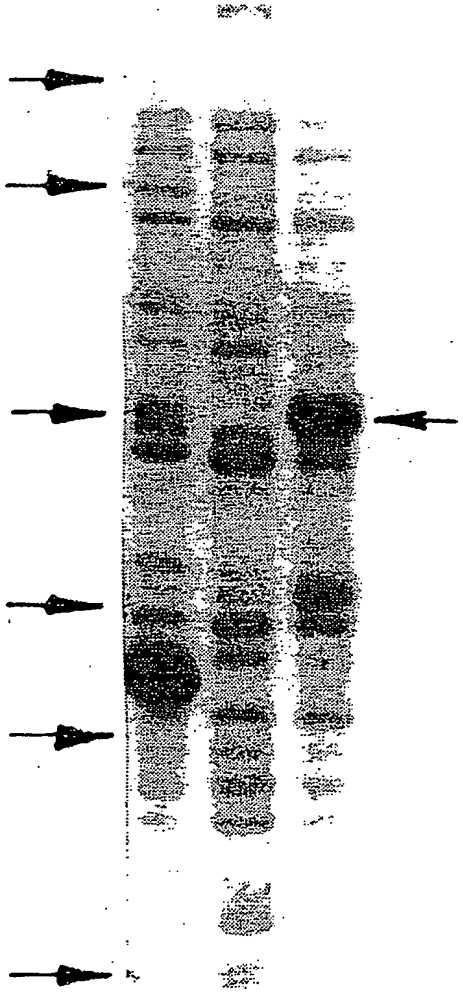


FIG. 6

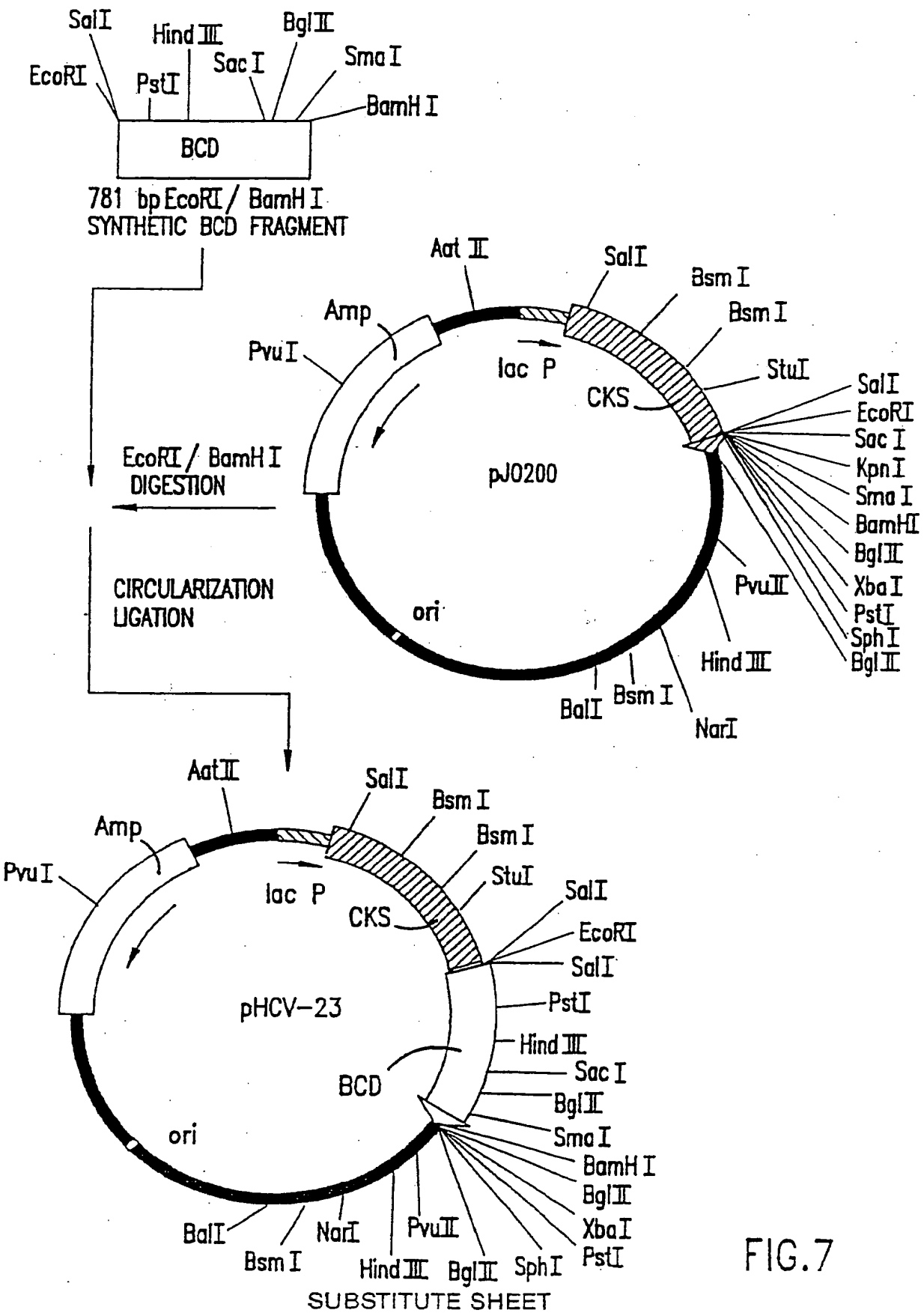


FIG.7

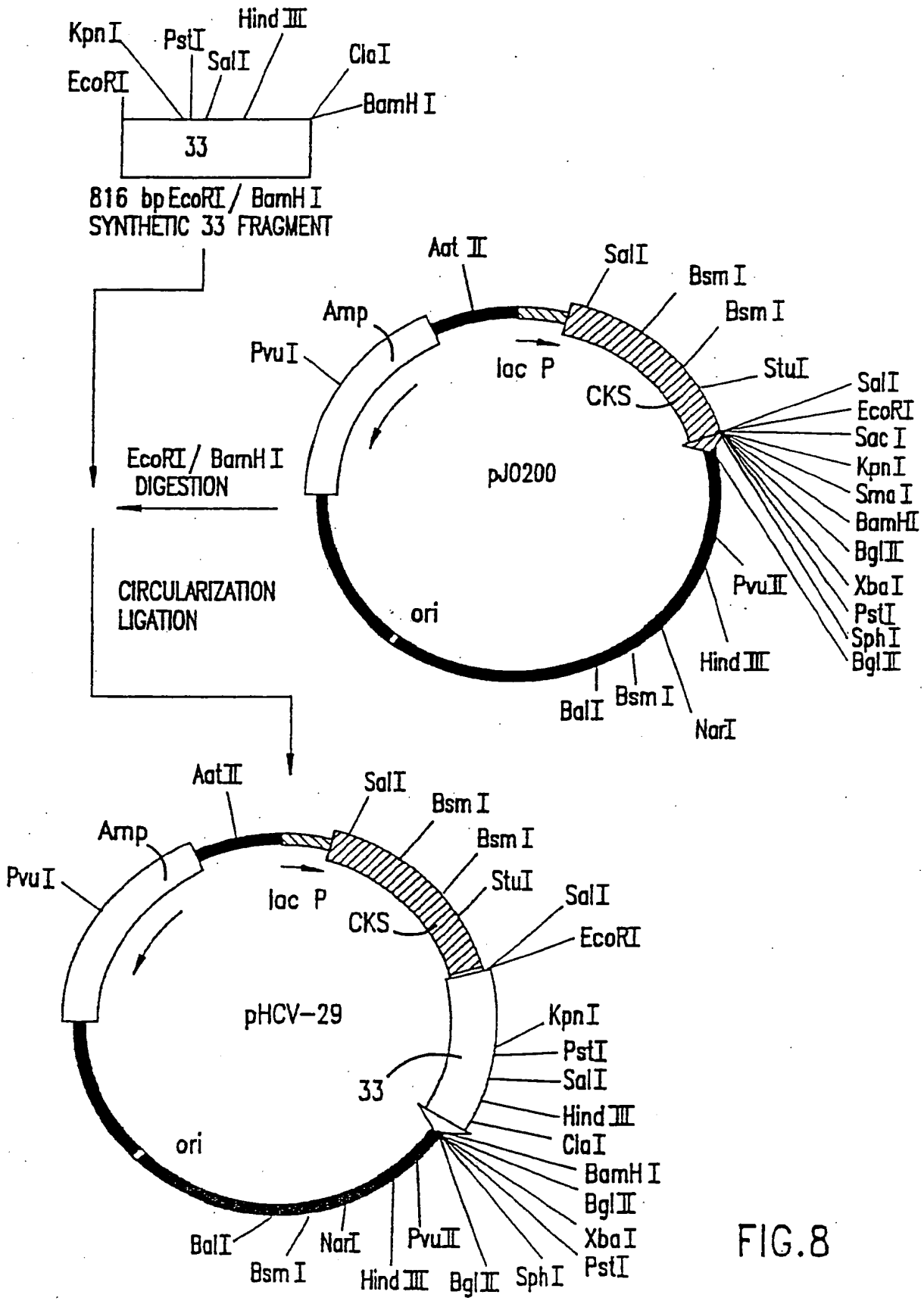
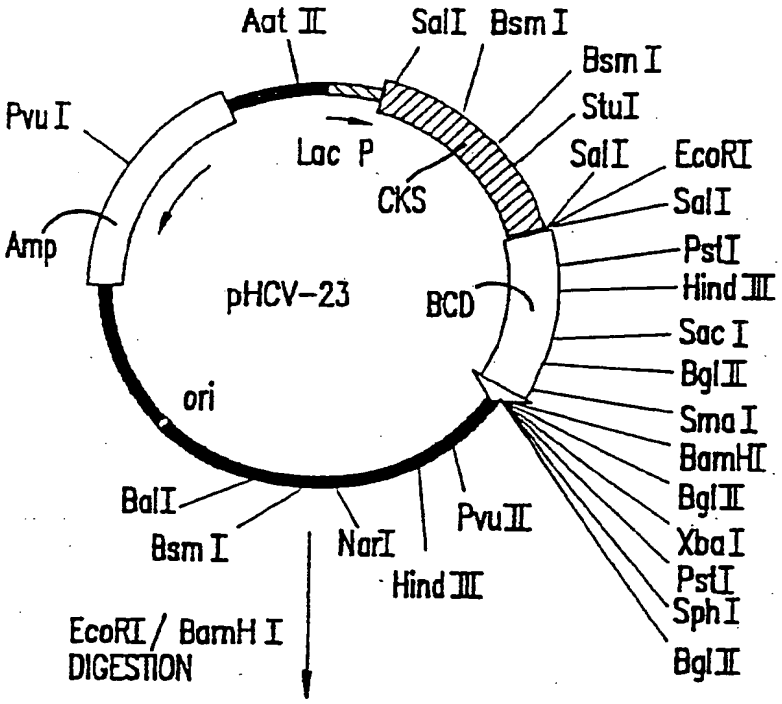
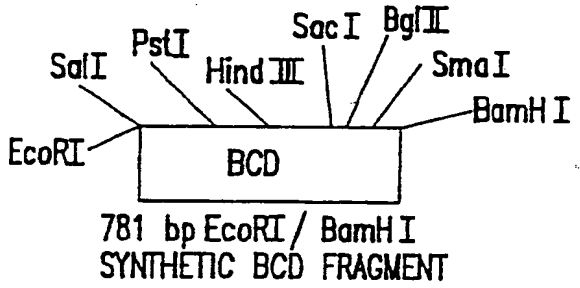
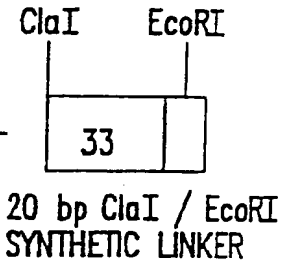


FIG.8







LINKER
ADAPTATION

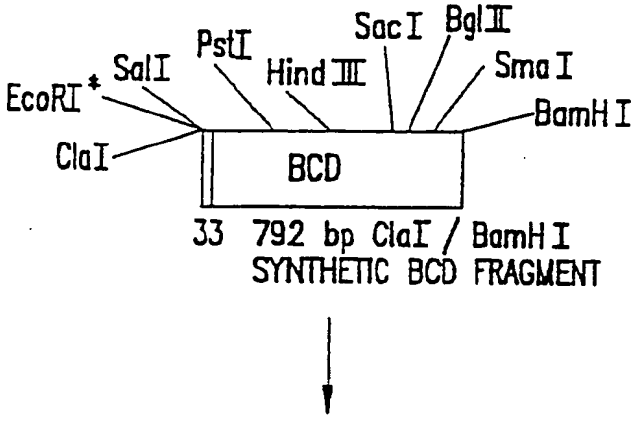


FIG.9

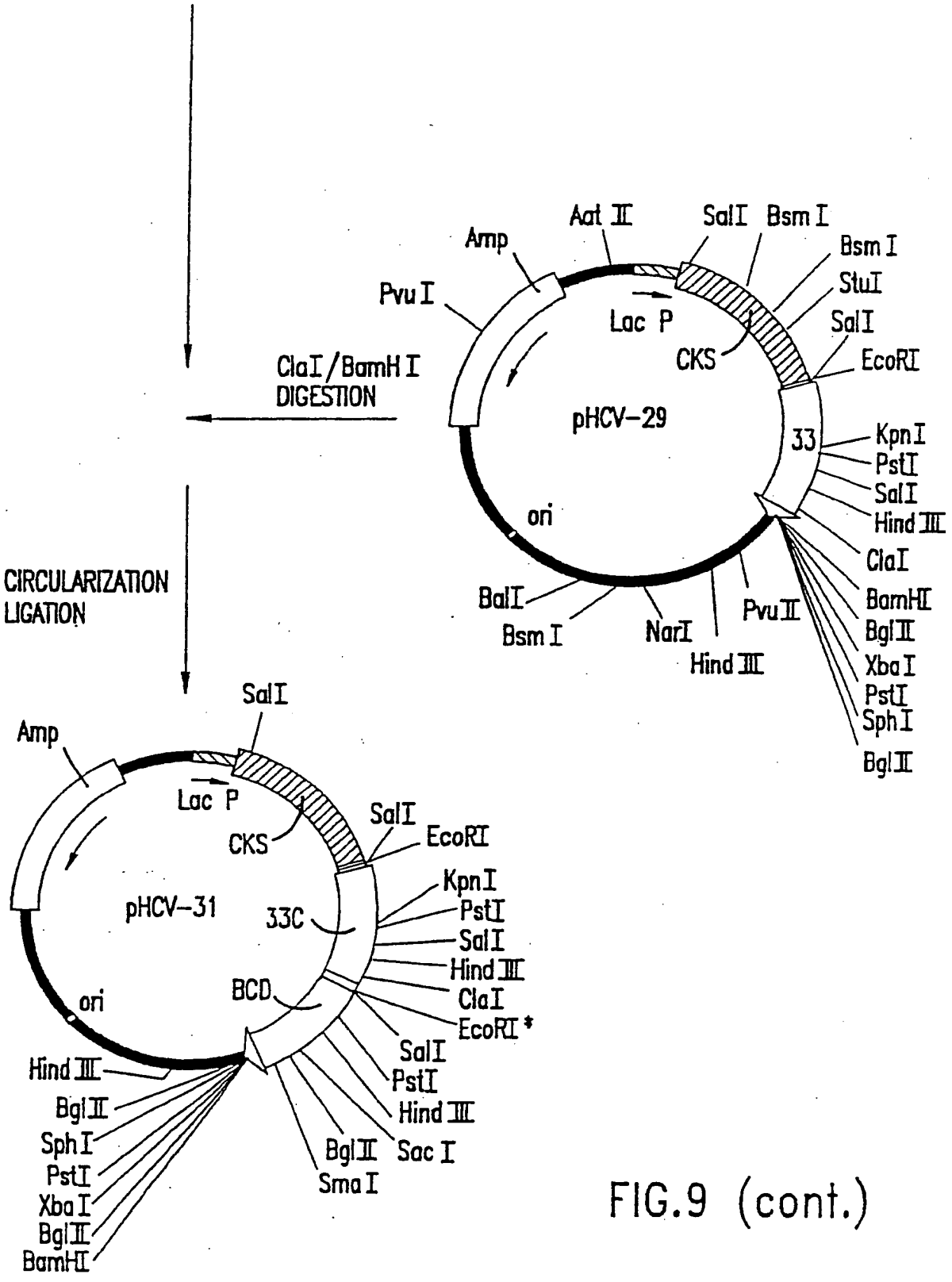


FIG.9 (cont.)

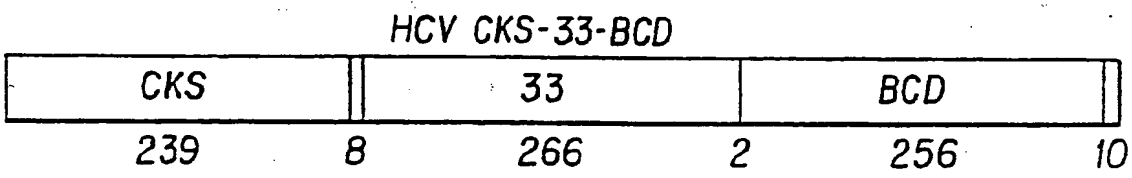


FIG. 10

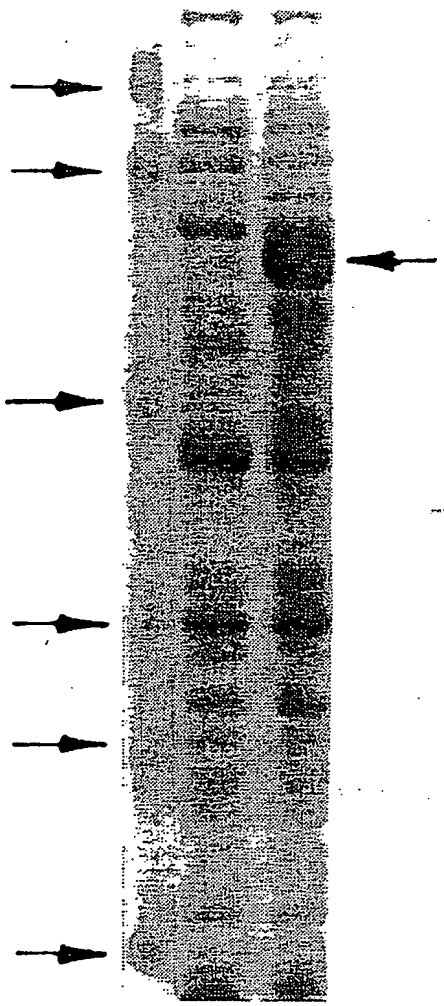


FIG. 11

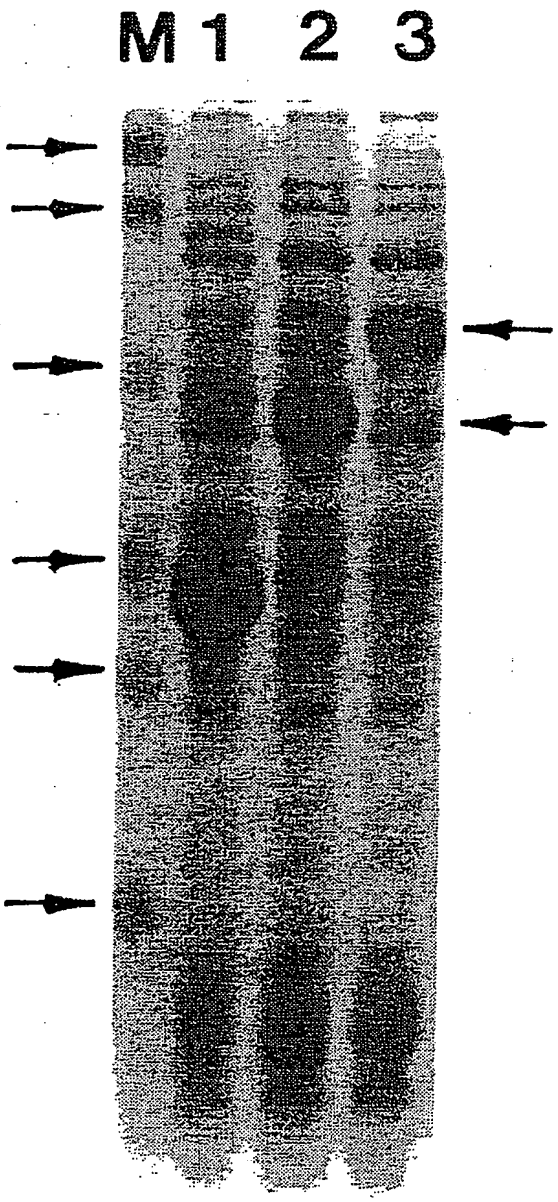


FIG. 12

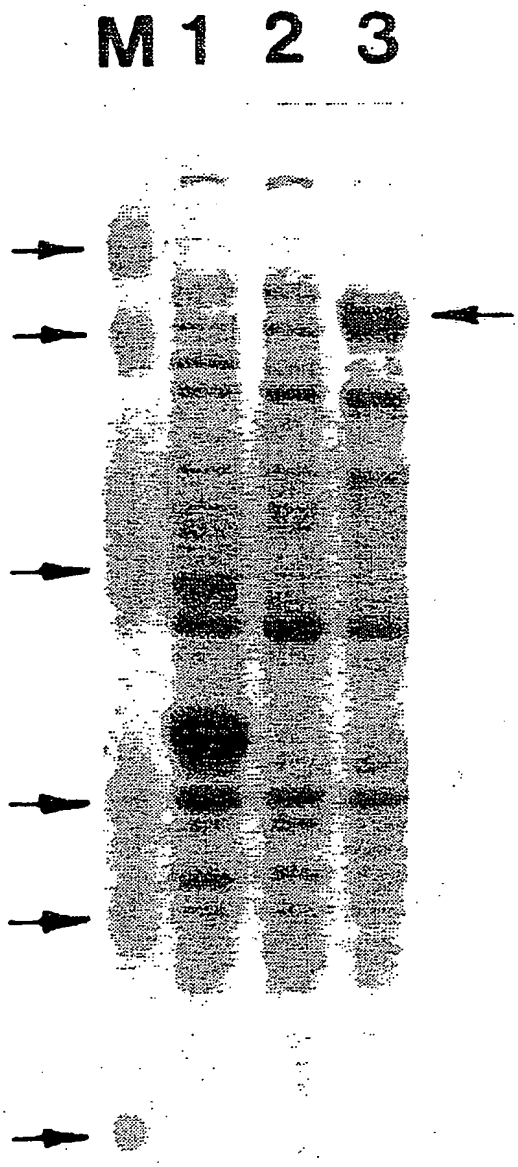


FIG. 13

	ASSAY WITH C100-3	ASSAY WITH pHCV-31 pHCV-34	
SAMPLE	MANUAL S/CO	MANUAL S/CO	CONFIRMATORY RESULTS
1	>5.88 (+)	>5.65 (+)	+
2	0.63	0.54	
3	>5.88 (+)	>5.65 (+)	+
4	>5.88 (+)	>5.65 (+)	+
5	0.43	0.46	
6	>5.88 (+)	>5.65 (+)	+
7	0.46	0.61	
8	0.41	0.70	
9	1.87 (+)	1.83 (+)	+
10	0.35	4.88 (+)	+
11	0.48	0.49	
12	0.32	0.50	
13	0.48	0.83	
14	0.37	0.37	
15	>5.88 (+)	>5.65 (+)	+
16	>5.88 (+)	>5.65 (+)	+
17	0.34	0.44	
18	3.01 (+)	2.33 (+)	+
19	0.74	0.72	
20	0.53	0.76	
21	>5.88 (+)	>5.65 (+)	+
22	0.24	0.30	
23	>5.88 (+)	>5.65 (+)	+
24	0.69	0.84	
25	0.50	0.75	
26	3.41 (+)	2.38 (+)	+
27	0.62	0.82	
28	0.61	0.53	
29	0.34	4.94 (+)	+
30	1.58 (+)	1.85 (+)	+
31	0.32	0.52	
32	>5.88 (+)	>5.65 (+)	+
33	0.45	0.58	

FIG. 14

34	>5.88 (+)	>5.65 (+)	+
35	>5.88 (+)	>5.65 (+)	+
36	0.37	0.44	
37	0.40	0.40	
38	>5.88 (+)	>5.65 (+)	+
39*	0.40	1.10 (+)	-
40	0.53	0.63	
41	0.41	0.34	
42	0.52	0.70	
43	0.28	0.44	
44	0.44	0.70	

$$S/CO = \frac{\text{Sample OD}}{\text{Cutoff OD}}$$

S/CO = <1.0 is non-reactive

S/CO = ≥1.0 is reactive

*This specimen was negative when retested in duplicate. (S/CO values 0.56 and 0.51.)

FIG. 14 CONT

PANEL MEMBER (LOT #)	IDENTITY	ASSAY WITH C-100-3	ASSAY WITH pHCV-31 AND pHCV-34	ORTHO ELISA	CONFIRMATORY RESULTS
		SAMPLE TO CUTOFF VALUES			
701	WEAK REACTIVE	1.819 (+)	4.469 (+)	1.239 (+)	+
702	BORDERLINE REACTIVE	1.711 (+)	4.738 (+)	1.130 (+)	+
703	NEGATIVE	0.443	0.348	0.256	-
704	WEAK REACTIVE	2.220 (+)	4.738 (+)	1.639 (+)	+
705	BORDERLINE REACTIVE	1.648 (+)	1.736 (+)	0.911	+
706	NEGATIVE	0.221	0.369	0.340	-
707	STRONG REACTIVE	5.713 (+)	4.738 (+)	4.272 (+)	+
708	STRONG REACTIVE	5.713 (+)	4.738 (+)	4.272 (+)	+
709	NON-REACTIVE*	0.401	0.533	0.650	-
710	NON-REACTIVE*	0.582	0.419	0.423	-

*CONTAINS VERY LOW LEVELS OF ANTI-HCV. NOT REQUIRED TO BE DETECTED BY CURRENT HCV ASSAYS.

FIG.15

ANTI - HCV RESULTS ON NON-A, NON-B HEMODIALYSIS PATIENTS

PATIENT #	DATE	ALT IU/L	ASSAY WITH C-100-3	ASSAY WITH pHCV-31, pHCV-34	CONFIRMATORY RESULTS
1	10/28/85	474	0.30 (-)	2.12 (+)	+
	11/11/85	113	0.38 (-)	4.72 (+)	+
	12/03/85	86	3.13 (+)	>5.65 (+)	+
	01/09/86	142	>5.61 (+)	NT	NT
	03/19/86	90	>5.61 (+)	>5.65 (+)	+
	09/30/86	25	>5.61 (+)	>6.67 (+)	+
2	09/14/87	217	5.02 (+)	5.84 (+)	+
	09/17/87	210	>5.61 (+)	6.58 (+)	+
3	10/02/87	116	1.61 (+)	1.69 (+)	+
4	11/24/87	NA	0.41 (-)	2.13 (+)	+
	12/17/87	NA	0.47 (-)	1.27 (+)	+
	01/13/88	NA	0.46 (-)	1.56 (+)	+
	02/21/88	NA	0.34 (-)	1.45 (+)	+
7	10/02/85	298	0.79 (-)	2.94 (+)	+
	10/07/85	548	0.86 (-)	2.68 (+)	+
	10/23/85	334	2.06 (+)	2.32 (+)	+
10	01/25/89	NA	0.57 (-)	2.66 (+)	+
	02/01/89	NA	1.08 (+)	2.80 (+)	+
	02/08/89	NA	1.75 (+)	3.38 (+)	+
	02/23/89	NA	2.22 (+)	2.56 (+)	+
	03/01/89	NA	1.94 (+)	3.21 (+)	+
	03/08/89	NA	1.64 (+)	2.52 (+)	+
	03/22/89	NA	1.49 (+)	1.76 (+)	+
	04/12/89	NA	2.69 (+)	5.29 (+)	+
	04/26/89	NA	2.77 (+)	>5.65 (+)	+
	05/17/89	NA	2.19 (+)	2.82 (+)	+
13	10/05/88	NA	0.31 (-)	0.51 (-)	NT
	10/19/88	NA	0.40 (-)	0.61 (-)	NT
	10/28/88	NA	0.33 (-)	0.53 (-)	NT
	11/09/88	NA	0.33 (-)	0.64 (-)	NT
	11/11/88	NA	0.37 (-)	0.66 (-)	NT

FIG. 16

	11/18/88	NA	0.42 (-)	0.57 (-)	NT
	11/25/88	NA	0.44 (-)	0.65 (-)	NT
	12/05/88	NA	0.51 (-)	0.74 (-)	NT
	12/16/88	NA	0.28 (-)	0.68 (-)	NT
	12/23/88	NA	0.29 (-)	0.64 (-)	NT
	01/04/89	NA	0.29 (-)	0.77 (-)	NT
	01/13/89	NA	0.33 (-)	1.11 (+)	+
	01/20/89	NA	0.30 (-)	1.11 (+)	+
	02/08/89	NA	0.26 (-)	1.81 (+)	+
	02/10/89	NA	0.26 (-)	1.88 (+)	+
	02/17/89	NA	0.26 (-)	2.23 (+)	+
	02/24/89	NA	0.28 (-)	3.75 (+)	+
	03/08/89	NA	0.28 (-)	5.25 (+)	+
	03/17/89	NA	0.22 (-)	>5.65 (+)	+
	04/03/89	NA	0.26 (-)	>5.65 (+)	+
	04/14/89	NA	0.26 (-)	>5.65 (+)	+
	04/20/89	NA	0.29 (-)	>5.65 (+)	+
	04/28/89	NA	0.31 (-)	>5.65 (+)	+
	05/05/89	NA	0.28 (-)	>5.65 (+)	+
	07/03/89	NA	0.23 (-)	5.32 (+)	+
17	10/05/88	1454	0.53 (-)	0.95 (-)	NT
	10/20/88	612	0.57 (-)	2.04 (+)	+
	10/28/88	576	0.56 (-)	1.26 (+)	+
	11/09/88	306	0.54 (-)	1.39 (+)	+
	11/11/88	321	0.73 (-)	1.34 (+)	+
	11/18/88	341	0.83 (-)	1.43 (+)	+
	11/25/88	333	0.73 (-)	1.83 (+)	+
	12/05/88	232	0.75 (-)	1.92 (+)	+
	12/16/88	239	0.81 (-)	2.75 (+)	+
	12/23/88	198	1.20 (+)	3.42 (+)	+
	01/13/89	146	3.17 (+)	>5.65 (+)	+
	01/27/89	104	4.36 (+)	>6.67 (+)	+
	02/17/89	113	>5.61 (+)	>6.67 (+)	+
	02/24/89	120	>5.61 (+)	>6.67 (+)	+
18	01/13/89	112	>5.61 (+)	>5.65 (+)	+
	01/21/89	72	>5.61 (+)	>5.65 (+)	+
	01/28/89	181	>5.61 (+)	>6.67 (+)	+
	02/08/89	106	>5.61 (+)	>5.65 (+)	+

FIG. 16A

	02/18/89	82	>5.61 (+)	>5.65 (+)	+
	03/08/89	62	>5.61 (+)	>5.65 (+)	+
	03/18/89	41	>5.61 (+)	NT	NT
	03/25/89	37	>5.61 (+)	>5.65 (+)	+
	04/04/89	37	>5.61 (+)	>5.65 (+)	+
	04/15/89	35	>5.61 (+)	>5.65 (+)	+
	04/22/89	27	>5.61 (+)	>5.65 (+)	+
	04/29/89	24	>5.61 (+)	>5.65 (+)	+
	05/06/89	25	>5.61 (+)	>5.65 (+)	+
	07/03/89	31	>5.61 (+)	>5.65 (+)	+
19	02/17/89	NA	0.33 (-)	0.75 (-)	NT
	02/24/89	NA	0.35 (-)	0.62 (-)	NT
	03/08/89	NA	0.38 (-)	0.69 (-)	NT
	04/03/89	NA	0.13 (-)	0.87 (-)	NT
	04/14/89	NA	0.35 (-)	1.07 (+)	+
	04/21/89	NA	0.32 (-)	1.54 (+)	+
	04/28/89	NA	0.29 (-)	1.04 (+)	+
	05/05/89	NA	0.36 (-)	1.16 (+)	+
	07/03/89	NA	0.30 (-)	1.24 (+)	+

NT = Not Tested
NA = Not Available

FIG. 16B

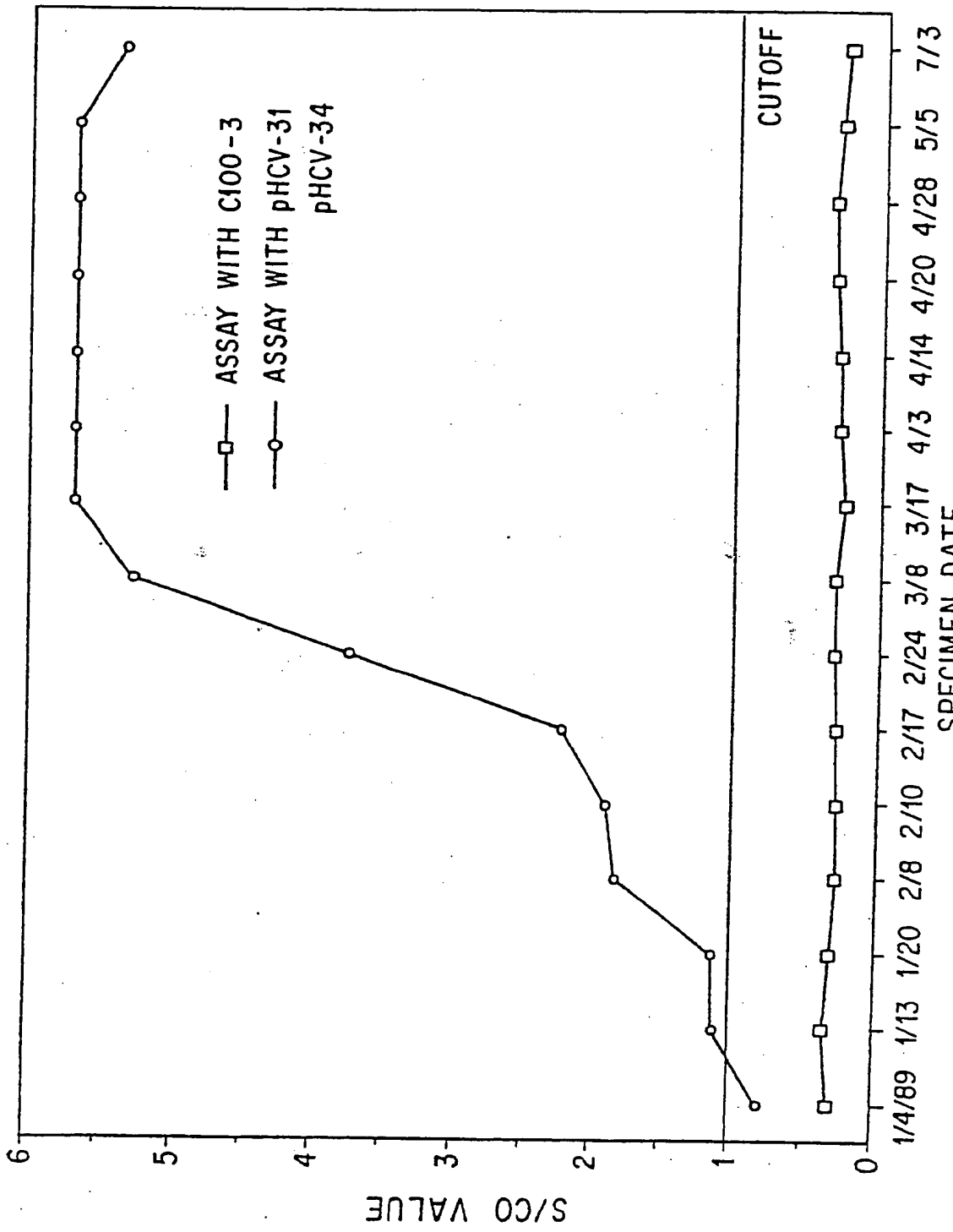


FIG. 17

CATEGORY	No. SPECIMENS	No. SPECIMENS REPEATABLY REACTIVE BY C-100-3 ASSAY	No. CONFIRMED	No. SPECIMENS REPEATABLY REACTIVE BY ASSAY WITH pHCV-31, pHCV-34	No. SPECIMENS REPEATABLY REACTIVE WHICH CONFIRMED (%)
ACUTE POST-TRANSFUSION NANBH	32	4 (12.50%)	4	14* (43.75%)	11/12** (91.67%)
COMMUNITY ACQUIRED NANBH (ACUTE)	10	2 (20.00%)	2	4 (40.00%)	4 (100.00%)

FIG. 18

CATEGORY	No. SPECIMENS FOUND ADDITIONALLY REACTIVE ASSAY pHCV-31, pHCV34	No. SPECIMENS CONFIRMED BY sp67 PEPTIDE	No. SPECIMENS CONFIRMED BY CORE PEPTIDE(sp75)	No. SPECIMENS CONFIRMED BY SOD-33c ANTIGEN
ACUTE POST-TRANSFUSION NANBH	11	0	8*	0
COMMUNITY ACQUIRED NANBH (ACUTE)	2	0	2	ND**

FIG. 19

CATEGORY	No. TESTED	C-100-3 ASSAY		pHCV-34, pHCV-31 ASSAY	
		REPEAT REACTIVE	CONFIRMED	REPEAT REACTIVE	CONFIRMED
CHRONIC ACTIVE NANBH	102	89 (87.3%)	88	98 (96.1%)	98
CHRONIC PERSISTENT NANBH	10	9 (90.0%)	9	9 (90.0%)	9
CHRONIC NANBH WITH CIRRHOSIS	17	15 (88.2%)	15	15 (88.2%)	15
CHRONIC NANBH (UNDEFINED)	35	25 (71.4%)	25	33 (94.3%)	33
TOTAL CHRONIC NANBH	164	138 (84.1%)	137	155 (94.5%)	155

FIG. 20

HCV POLYPEPTIDE SPOTTING CONDITIONS

PLASMID/PROTEIN	ng/SPOT	SPOTTING BUFFER
c100	100-150	20mM Tris-HCl, 0.9% NaCl, 0.015% SDS, pH 8.3
pHCV-23/CKS-BCD	100-150	20mM Tris-HCl, 0.9% NaCl, 0.015% SDS, pH 8.3
pHCV-29/CKS-33c	100-150	50mM Naphosphate, 0.01% Triton X100, pH 6.5
pHCV-34/CKS-CORE	75-100	50mM Naphosphate, 0.0025% Tween20, pH12.0

FIG. 21

	REFLECTANCE DENSITY VALUES		LIMITING DILUTION	
ANTIGEN	NEGATIVE MEAN	CUTOFF	A00642	423
c100-3	0.023	0.129	1600	40
pHCV-23	0.011	0.050	3200	320
pHCV-29	0.005	0.031	12800	2560
pHCV-34	0.027	0.166	400	320

FIG. 22

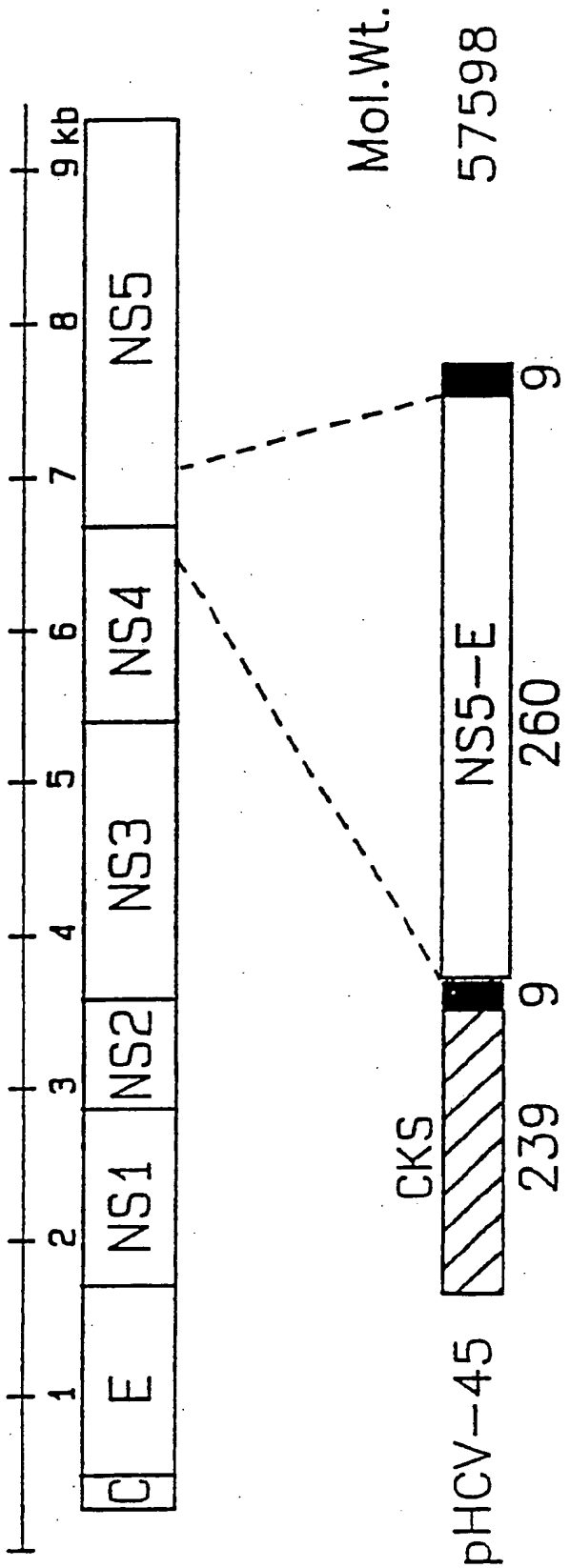


FIG. 23

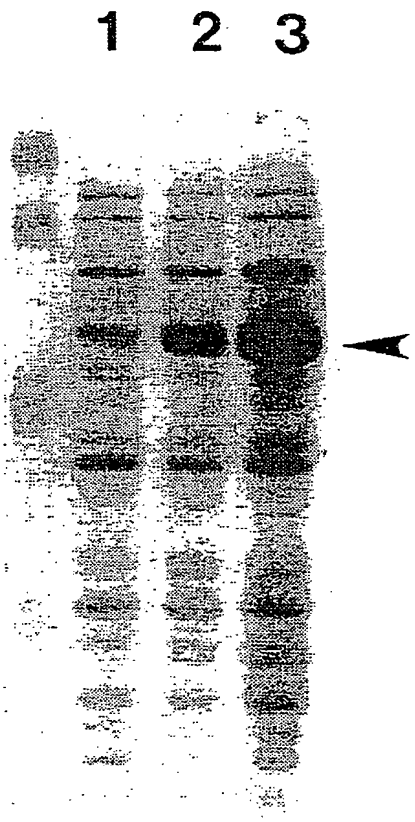


FIG. 24

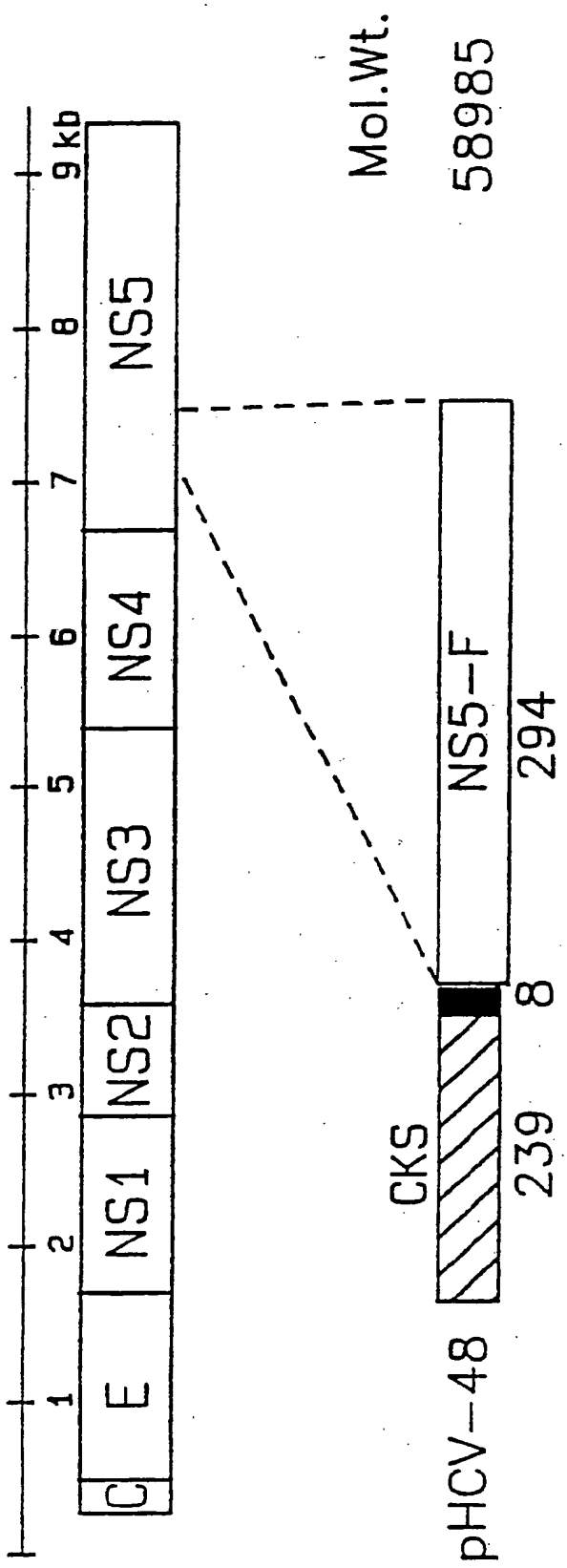


FIG. 25

1 2 3

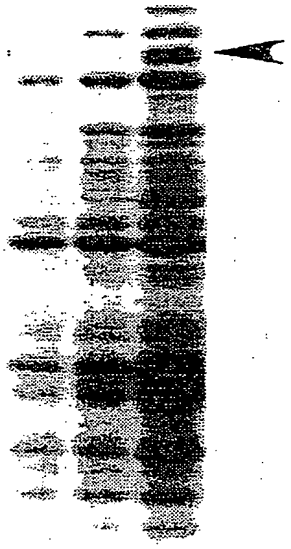


FIG. 26

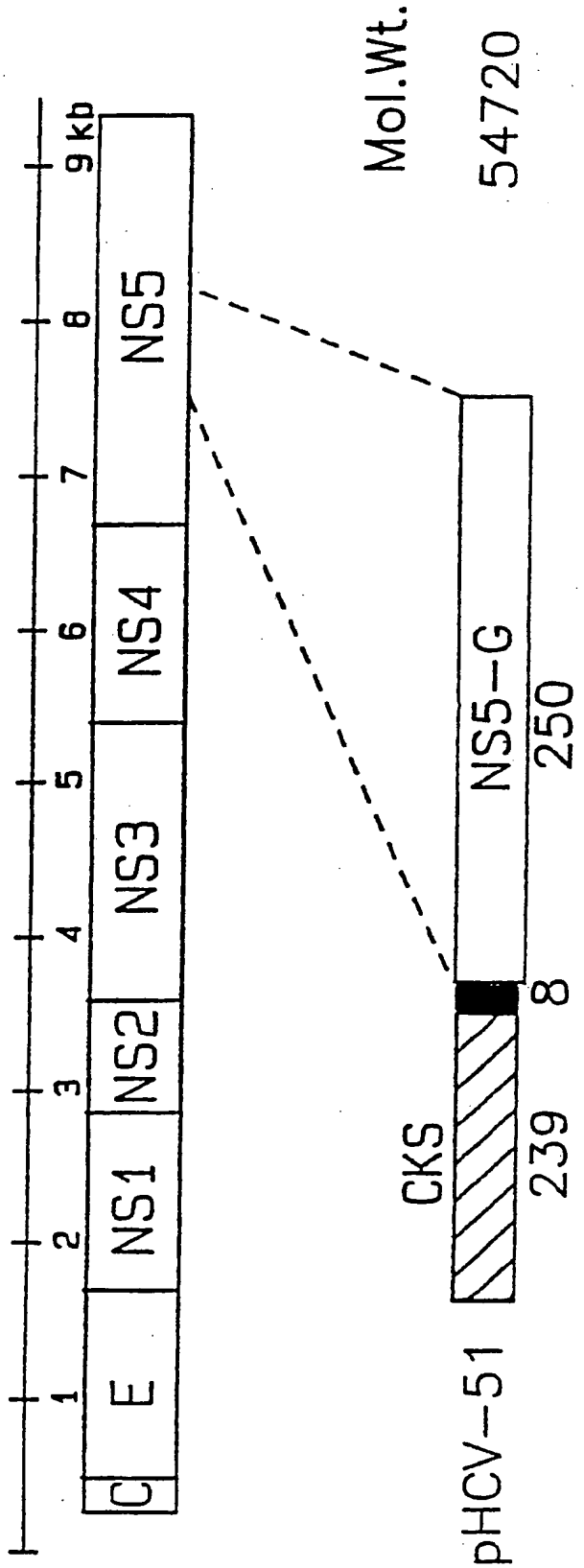


FIG. 27

1 2 3

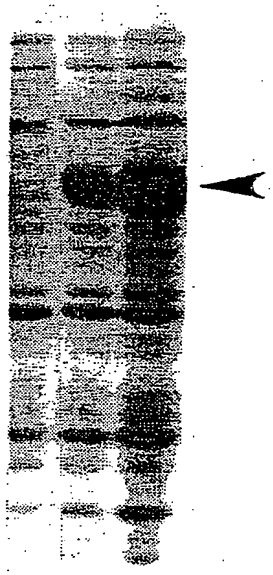


FIG. 28

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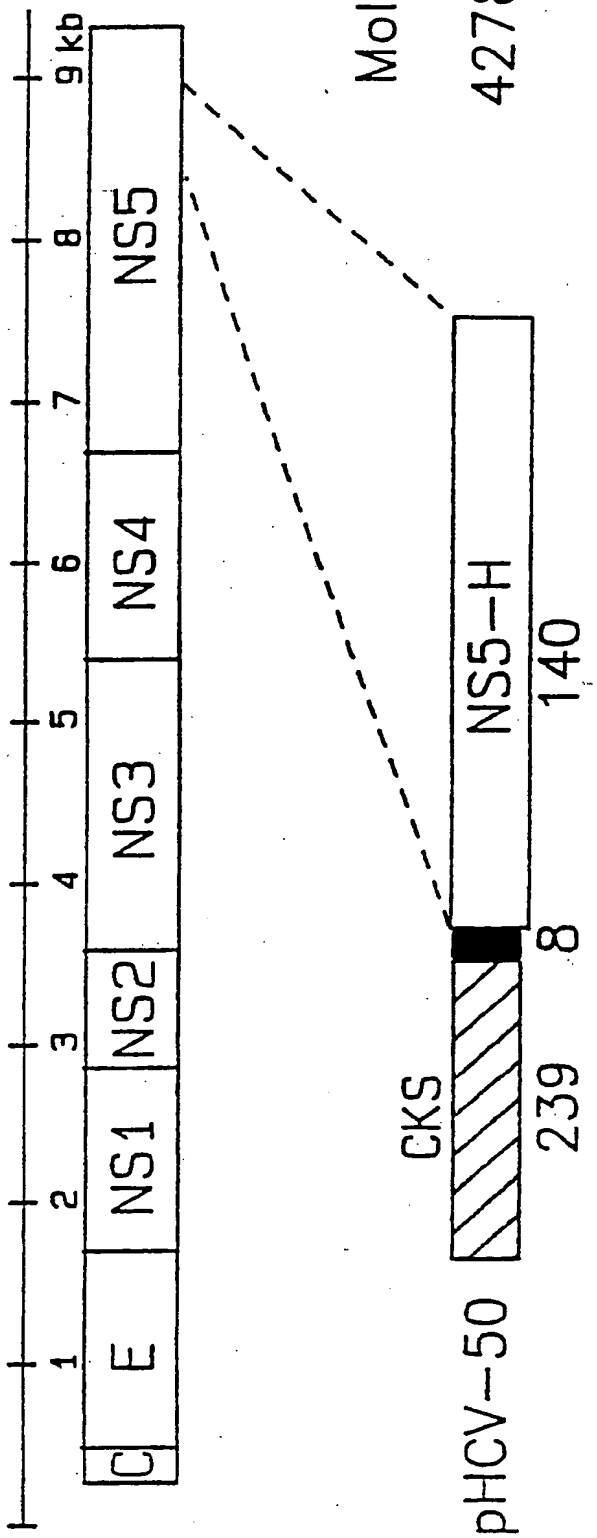

FIG. 29

1 2 3

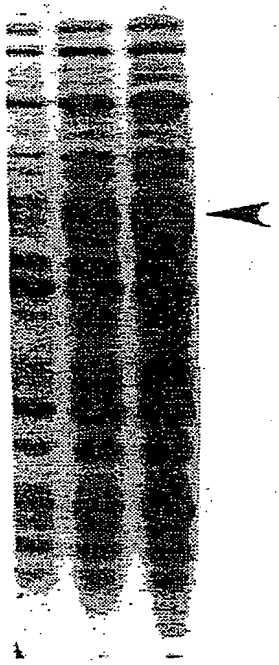

FIG. 30

34/48

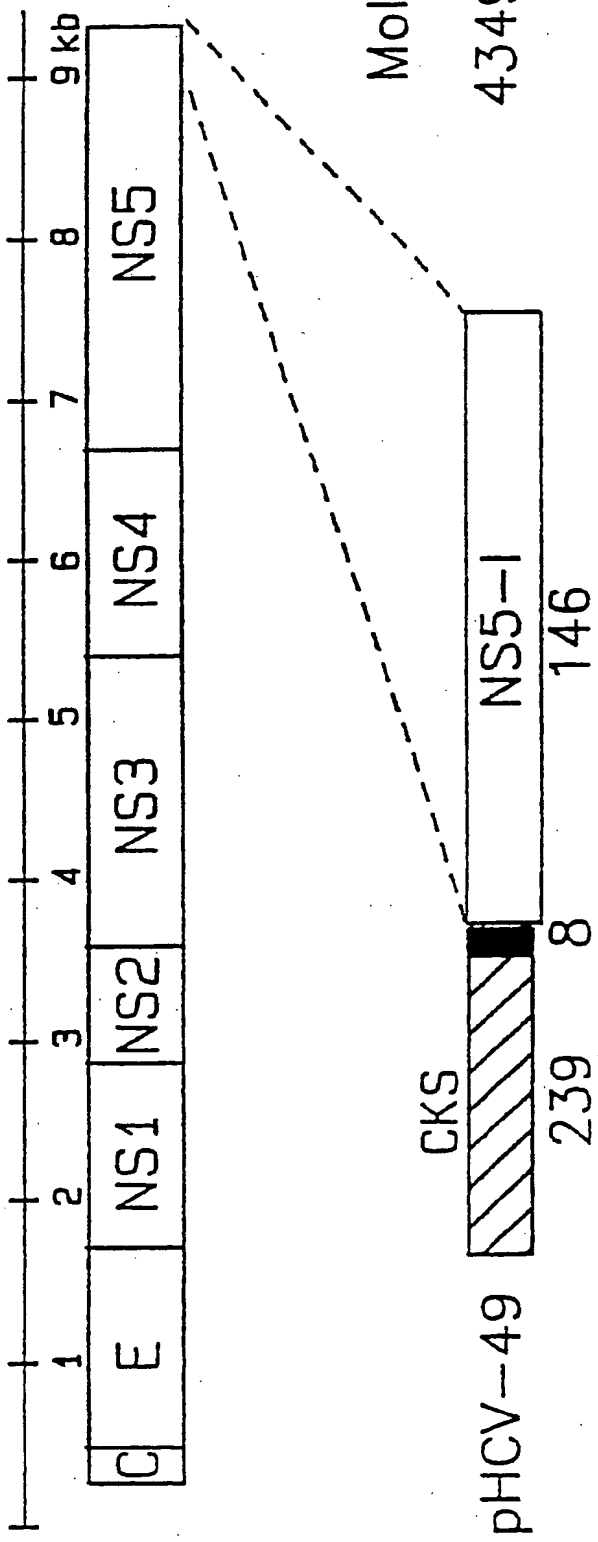

FIG. 31

1 2 3

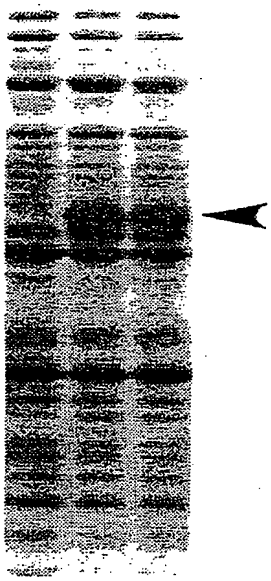

FIG. 32

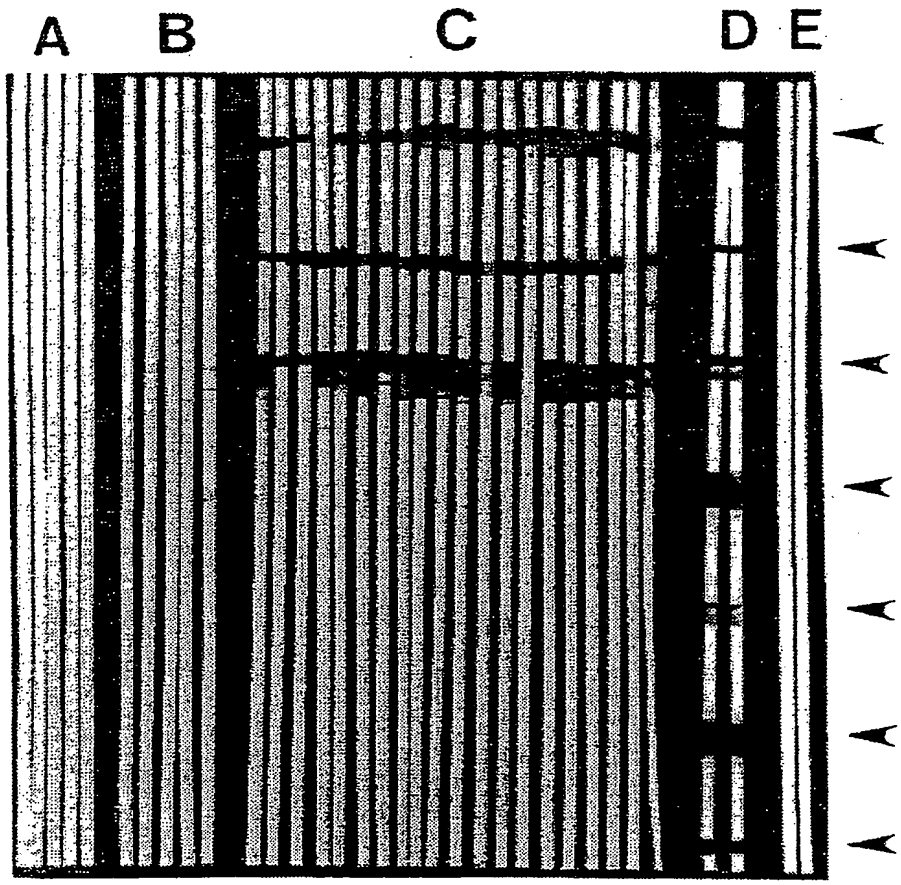

FIG. 33

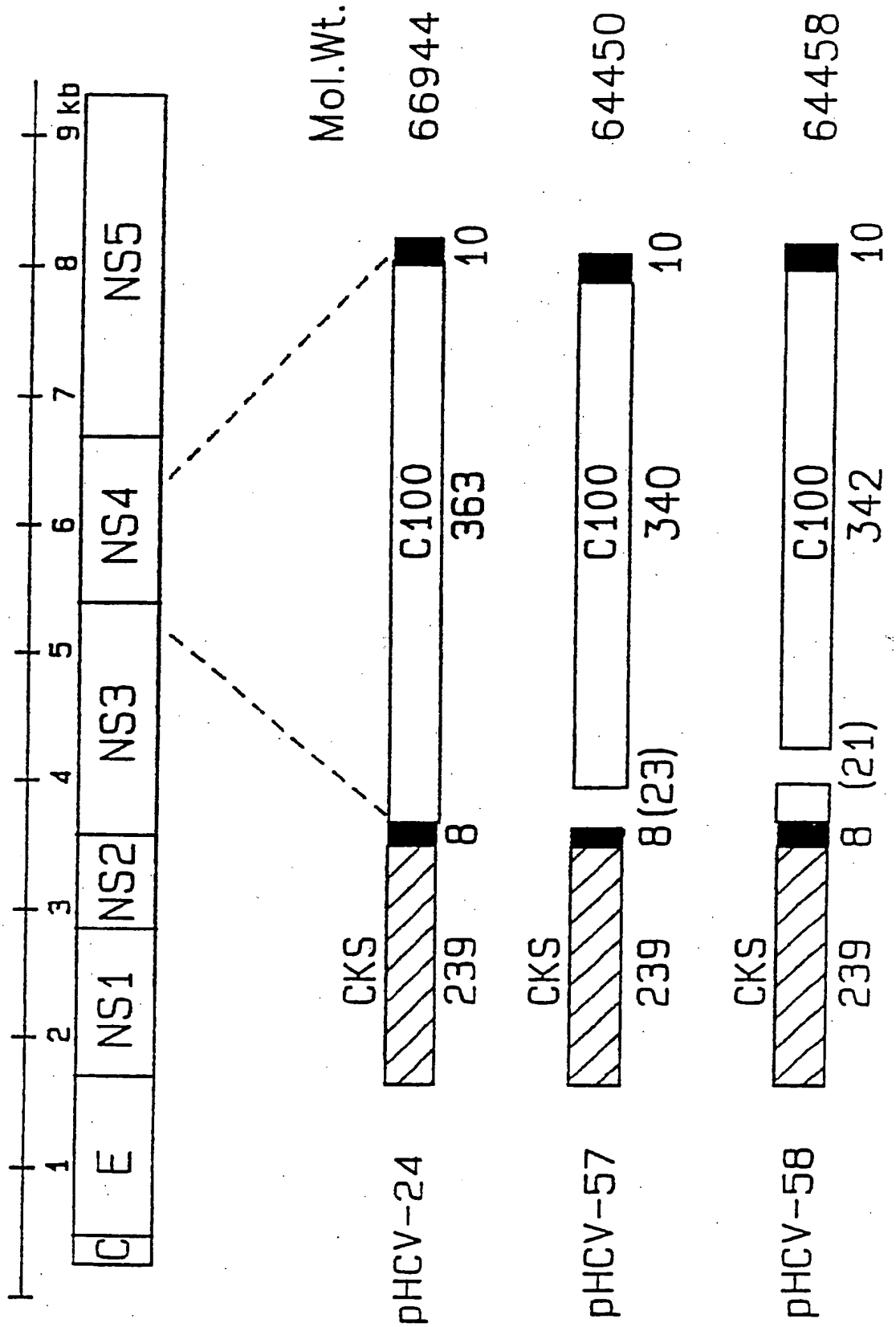

FIG. 34

1 2 3 4 5 6 7 8 9

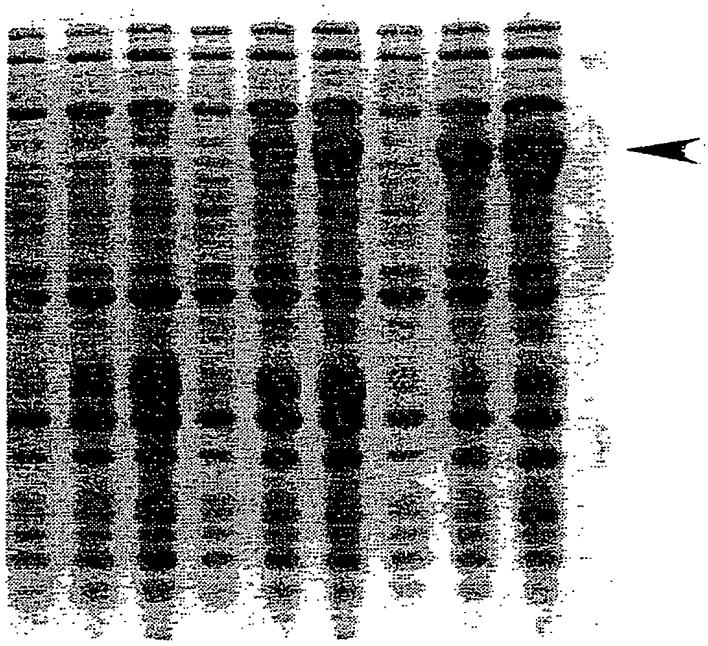

FIG. 35

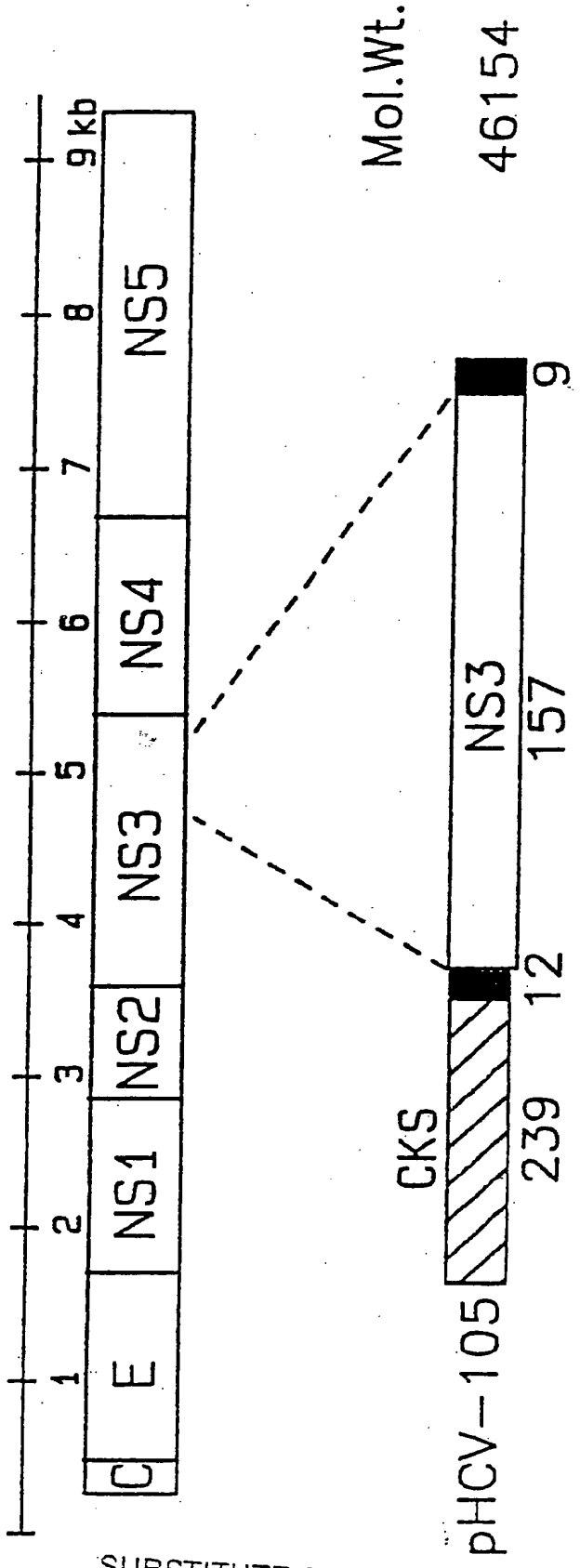

FIG. 36

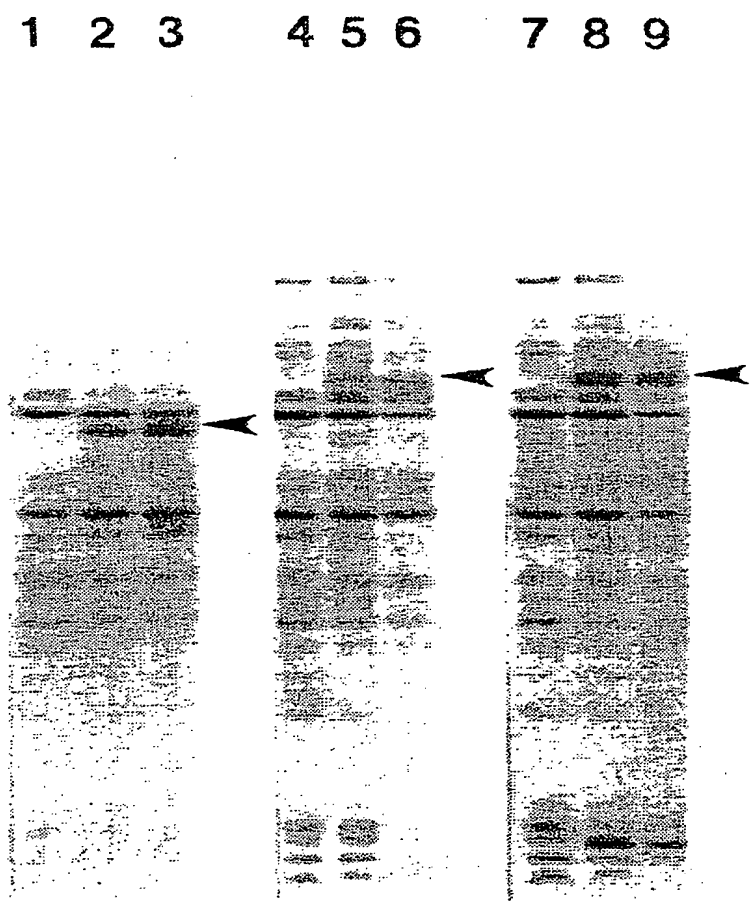

FIG. 37

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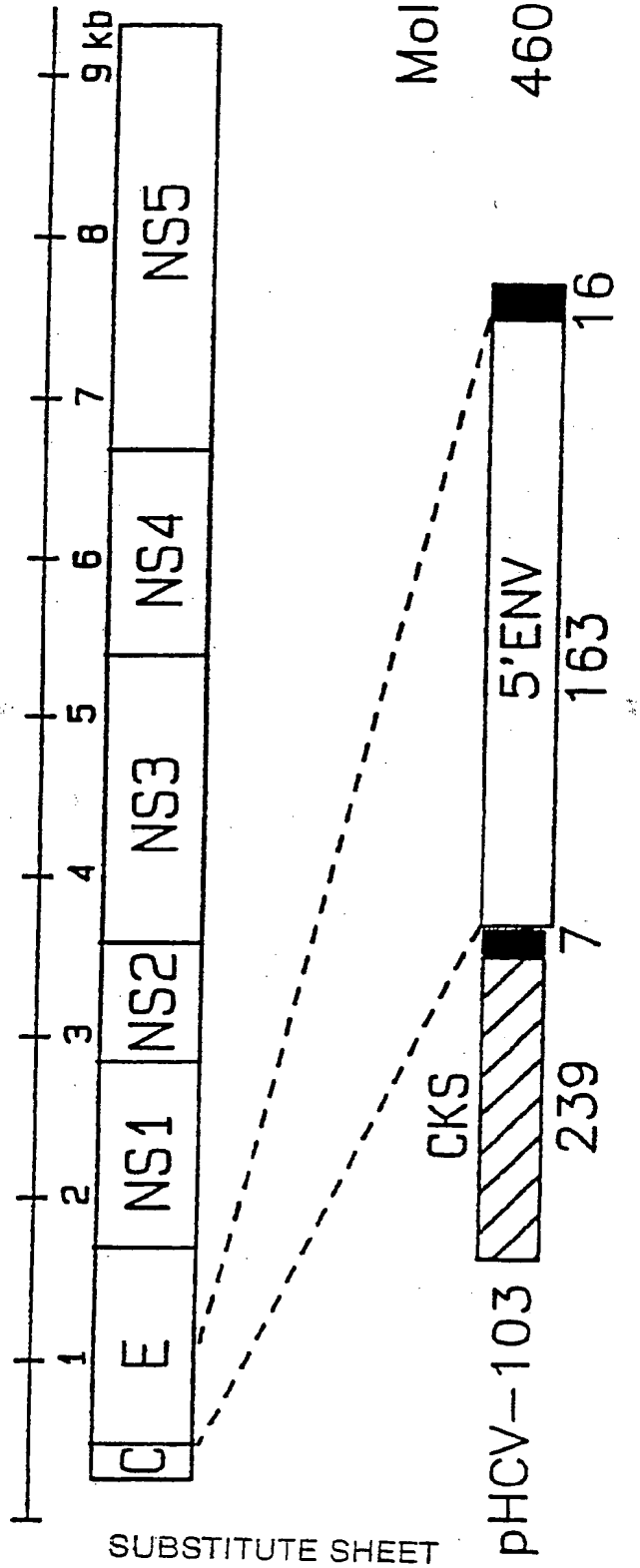

FIG. 38

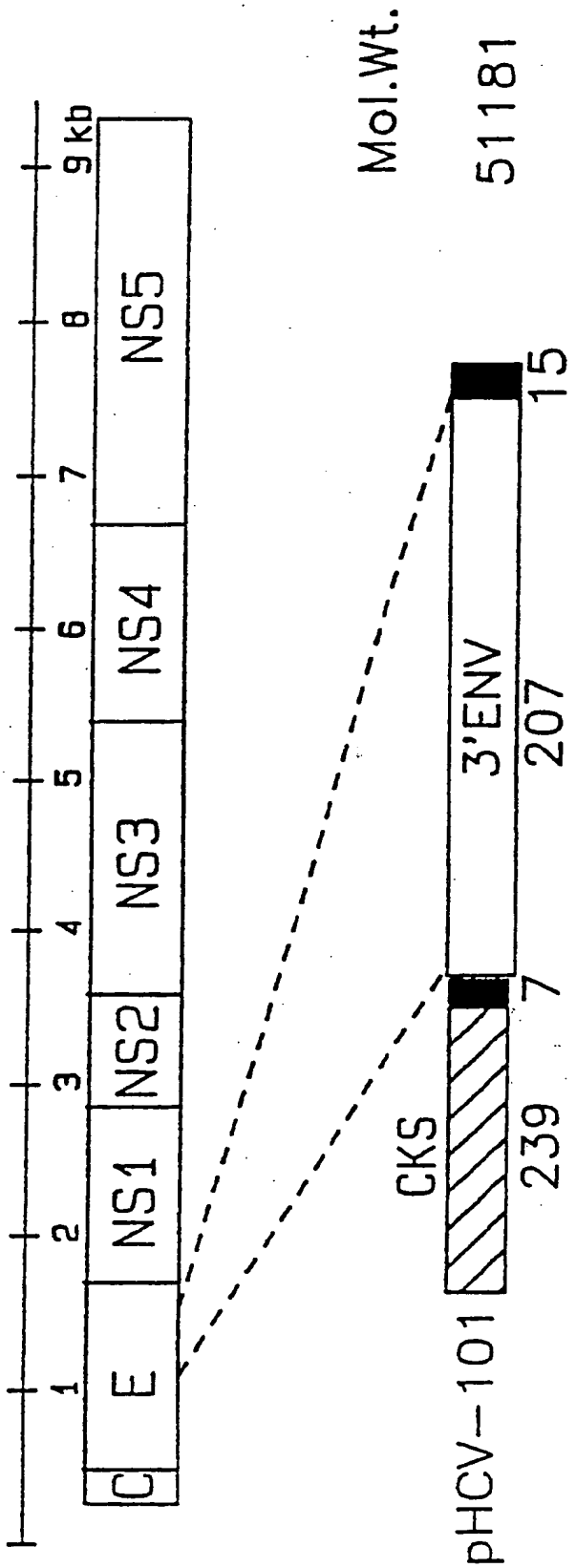

FIG. 39

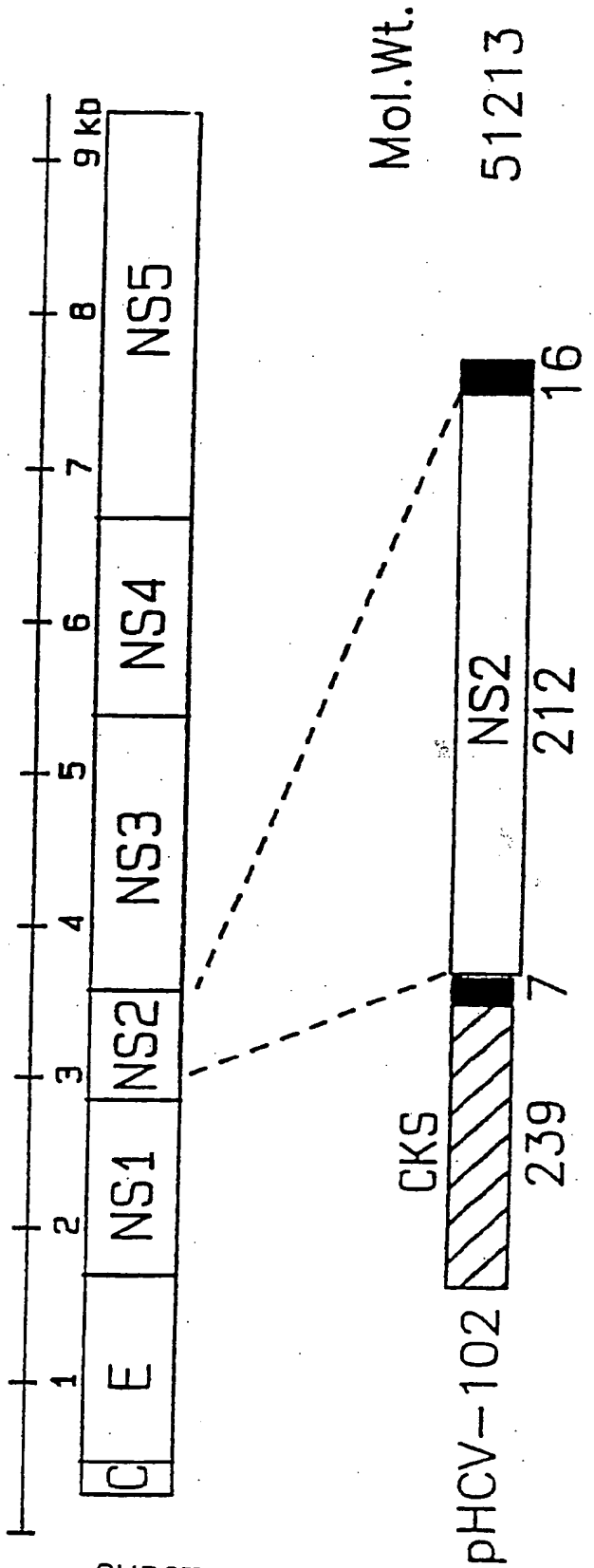

FIG. 40

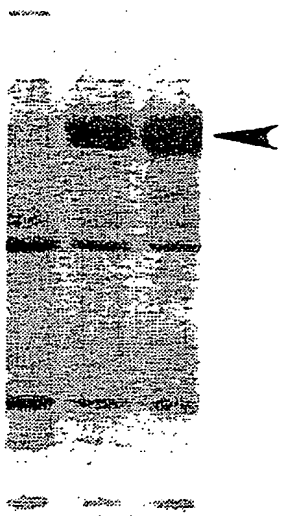

FIG. 41

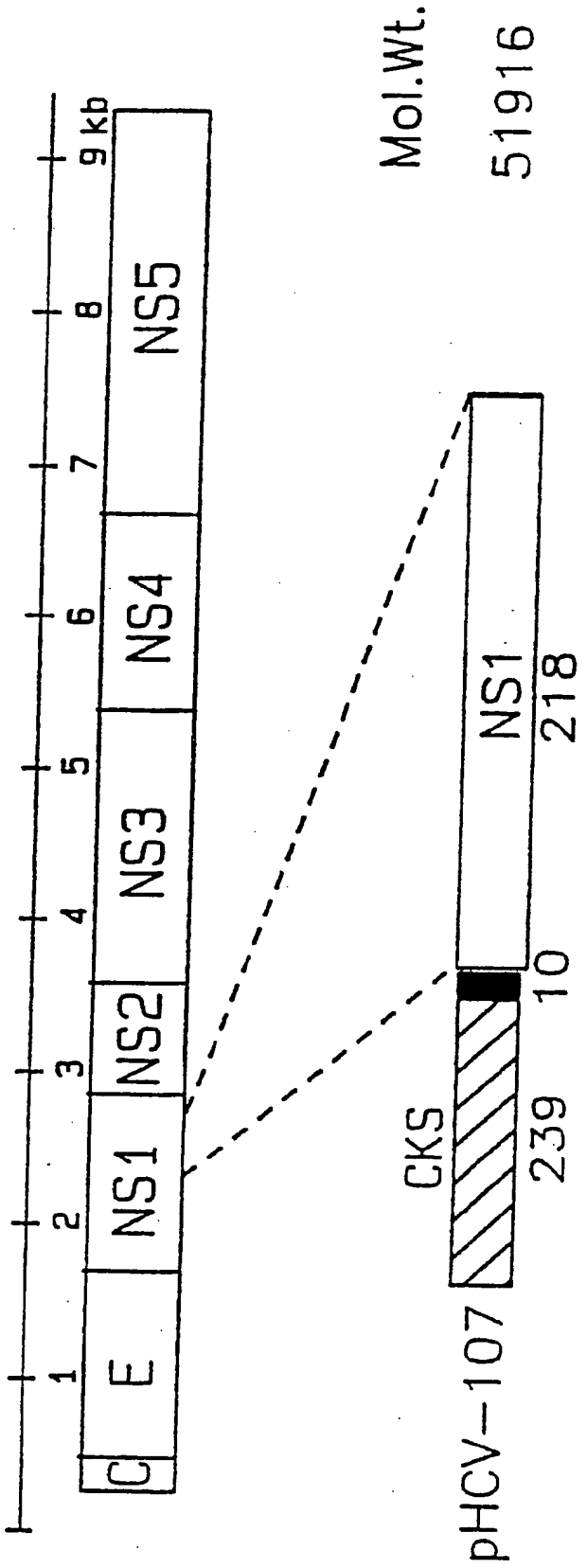

FIG. 42

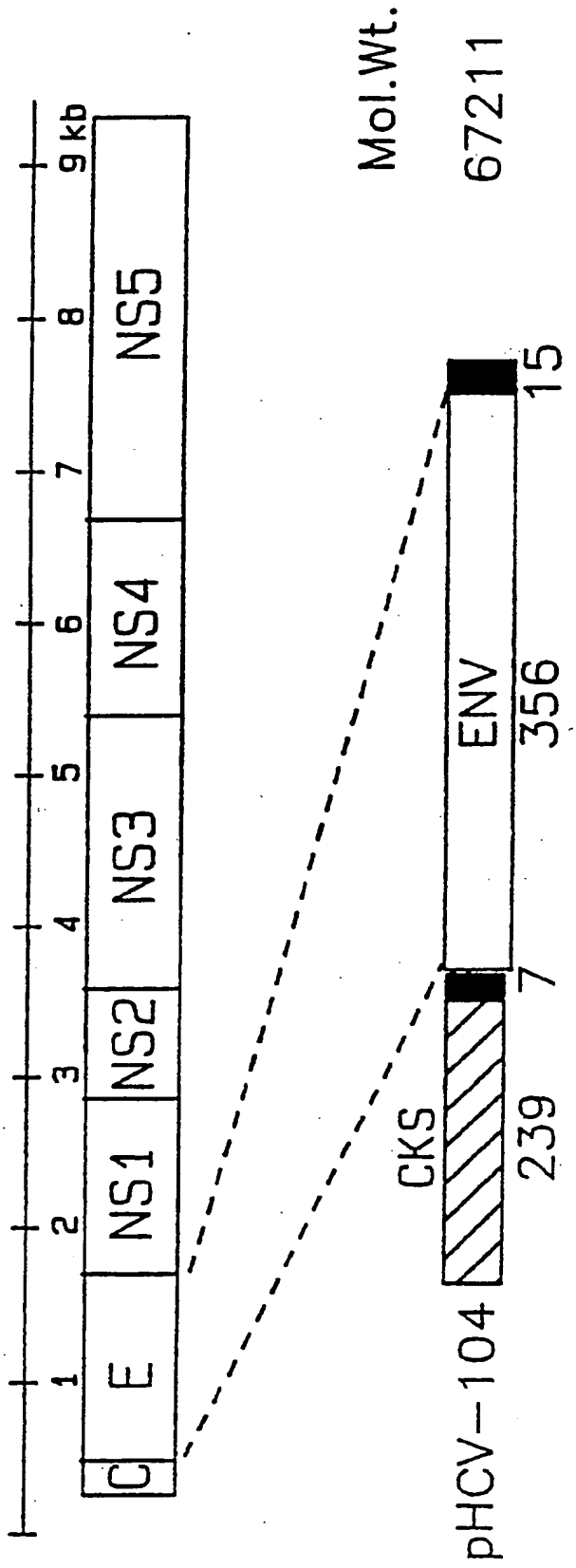

FIG. 43

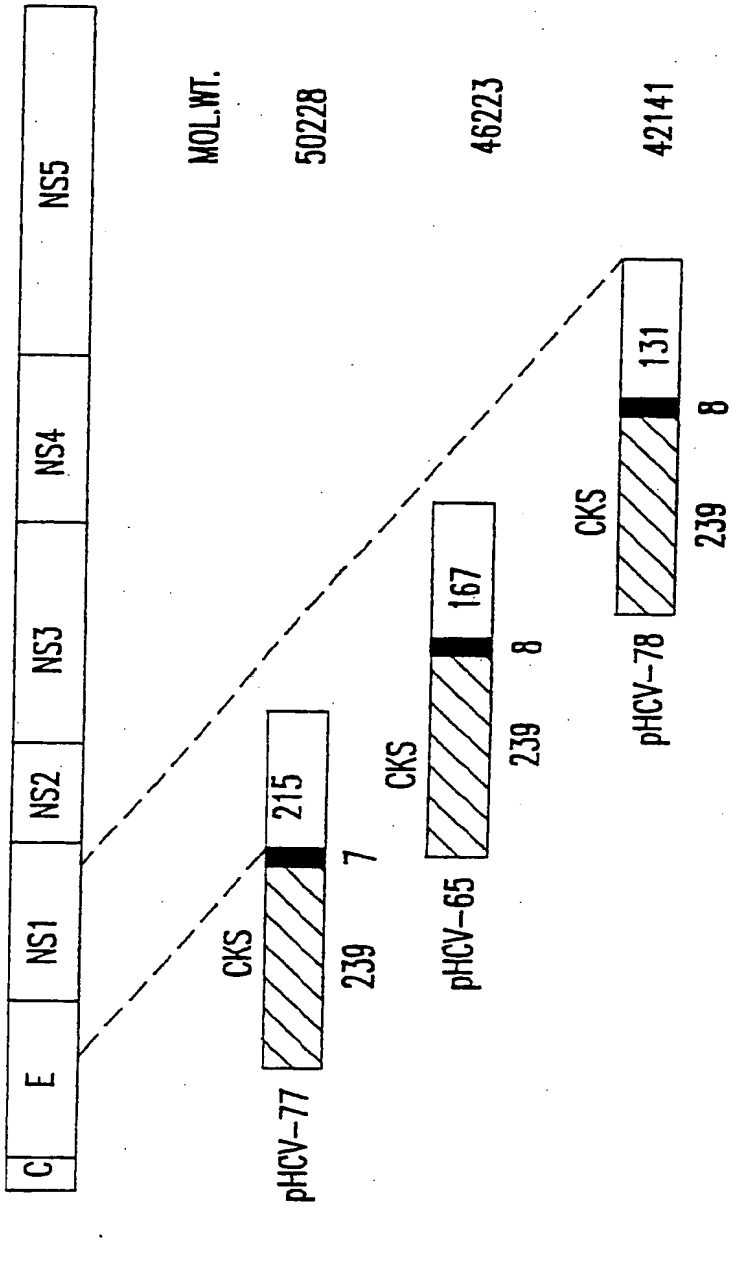

FIG.44

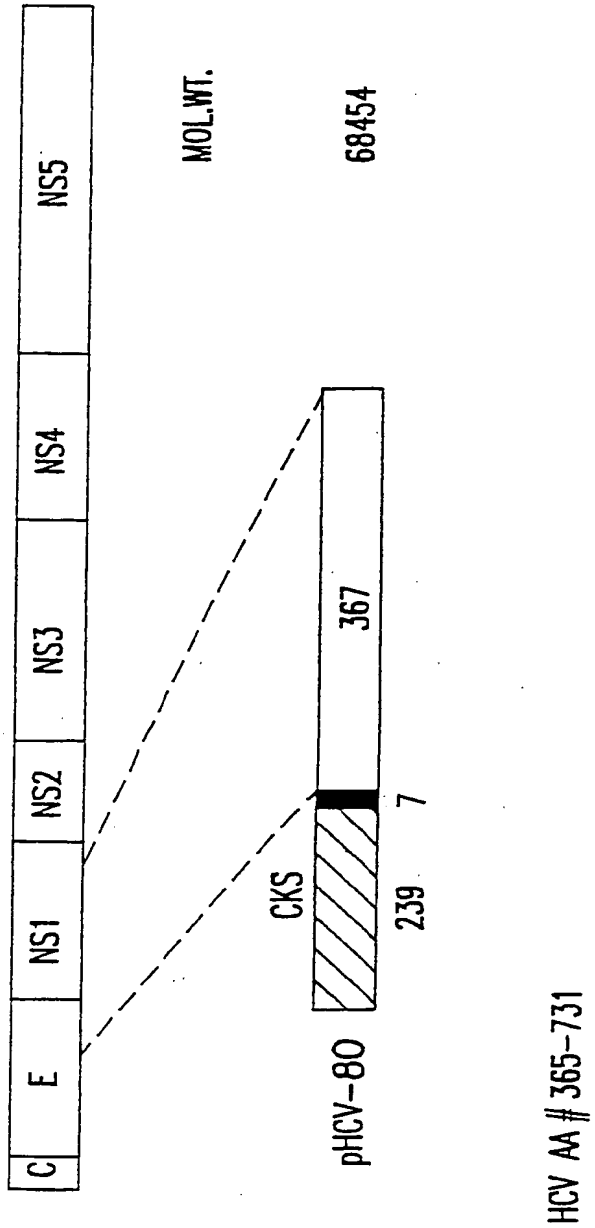

FIG.45

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/07188

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :C07K 15/00; C12Q 1/70
US CL :530/409; 435/5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/409, 826; 435/5, 7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PIR, GENESEQ, SWISS-PROT, WPI, APS, CA, MEDLINE
search terms: hepatitis C virus, HCV, CMP-KDO synthetase, CKS, fusion protein, NS1, assay, kit, diagnostic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,106,726 (Wang) 21 April 1992, see entire document.	1-19
Y	EP, A, 0,318,216 (Houghten) 31 May 1989, see entire document.	1-19
Y	EP, A, 0,388,232 (Houghten) 19 September 1990, see entire document.	1-19
Y	EP, A, 0,331,961 (Bolling et al.) 13 September 1989, see entire document.	1-19
Y	Proceedings of the National Academy of Sciences, Volume 88, issued March 1991, Q.-L. Choo et al., "Genetic Organization and Diversity of the Hepatitis C Virus", pp. 2451-2455, see entire document.	1-19
Y,P	Journal of General Virology, Volume 72, issued October 1991, D. Kremsdorf et al., "Partial Nucleotide Sequence Analysis of a French Hepatitis C Virus: Implications for HCV Genetic Variability in the E2/NS1 Protein", pp. 2557-2561, see entire document.	1-19

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
10 NOVEMBER 1992	25 NOV 1992
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer D. BARND
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-0196

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